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ALLERGIC FINDINGS IN EPILEPTIC PATIENTS AND ANCESTORS

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NO definite pathologic mechanism or other acceptable theory has thus far been able to explain fully the manifestations of so-called idiopathic epilepsy. These manifestations may include various types of convulsions, grand mal with tonic or clonic spasms; petit mal with momentary lapses of consciousness, with or without various forms of psychic equivalent symptoms or psychomotor seizures. In any of the types of seizures grouped as petit mal there may appear a modified state of amnesia and various forms of automatism. These various syndromes may occur without alteration of discoverable brain structure and remain largely clinically symptom complexes of disturbed metabolism with evidence of cerebral cortical irritation.

It is recognized that the biochemical metabolism of the body is necessarily altered by the presence of any toxic substance, provided it is of sufficient quantity or concentration to cause irritation of unstriped muscle fibers, with various disturbances of the sympathetic nervous system. The animal or human environment (soil) may thus be altered, resulting in the production of various symptoms, including "disturbed functioning of the rate-regulating mechanism of the brain," as pointed out by Berger,[2] i.e., a paroxysmal cerebral disrhythmia, as has been repeatedly shown by the more recent researches of Lennox, Gibbs and Davis,[5,9,10,11,12,13,14,17] with the confirmation of other recent investigators,[7,21,22] who have been using electroencephalogram recordings for brain site localization on patients with convulsions, or petit mal attacks, including various psychomotor seizures. The electroencephalogram recordings and wave patterns which are of real assistance and significance are not thus far definitely diagnostic of any of the types of epilepsy. It is necessary to depend on the clinical symptoms and biochemical laboratory findings in conjunction with the encephalogram recordings to make a diagnosis, as pointed out by Palmer and Hughes,[21] and more recently in a critical analysis of electroencephalogram studies on 626 cases of epilepsy by Finley and Dynes.[7]

As far as I have been able to learn, no electroencephalograms have been reported on a series of definitely recognized allergic individuals without convulsive seizures. Most investigators agree, however, that a cerebral edema produced by vasospasm is almost invariably an allergic phenomenon. In 1927 I reviewed a series of 100 consecutive cases of epilepsy[24] treated in private practice and summarized their histories and the clinical and laboratory findings. All so-called allergic manifestations which appeared in the patients, their ancestors, or brothers and sisters were noted. A number of other articles, to mention only a few,[1,3,4,6,8,15,16,18,19,20,25,26,27,28] have appeared on the possible relationship between allergy and certain types of convulsions and other periodic states of unconsciousness, with varied neurologic, and at times, semi-psychical symptoms.

Adamson and Sellers reported in the *Journal of Allergy*, May, 1933, on "Observations on the Incidence of the Hypersensitive State in 100 Cases of Epilepsy."[1] More recently D. C. Dewar in the *Journal of Mental Sciences*, London, October, 1941, wrote on "The Allergic Factor in Idiopathic Epilepsy."[6] He studied and carefully investigated twenty-four epileptic patients as to any allergic conditions in the patients and their ancestors. He reports finding evidence of allergy in the family history (one side or the other) in 66 per cent of twenty-four epileptic patients he studied; in 20 per cent there was a history of allergy on both sides of the family. He treated twelve of the twenty-four by elimination and specific desensitization.

In twenty-four (non-allergic) control cases he obtained a history of allergy on one side or the other of the family in 17 per cent—with none having a history of allergic manifestations on both sides of the family. He also investigated twenty-four psychotic patients, in 25 per cent of whom there was a history of allergy on one side or the other of the family ancestry, and none on both sides.

Dewar states that his investigations as a whole tended to confirm the postulated relationship of allergy and epilepsy. His supporting facts, briefly, are the following:

(1) The preponderance of allergic manifestations in the personal and family history of the epileptic as compared to psychotic and normal controls.
(2) Epileptics displayed, as a group, greater sensitivity on skin testing.
(3) Following desensitization, the skin sensitivities were lost or lessened in degree in every instance but one. This change in dermal responsiveness was accompanied in four patients by fewer seizures and increased mental acuity.
(4) In four patients the personal history suggested a linking of specific protein and seizures. It was worthy of note that in each instance a positive reaction resulted from skin testing the subject for the suspected allergen. In two cases positive reaction to cheese developed convulsions with specific desensitization, and in another the patient died after a fifth injection of the specific antigen.
(5) Treatment directed by elimination and *specific* desensitization was successful in alleviating symptoms in nine of twelve patients thus treated. The intramuscular route was considered to give excellent results, provided the precaution was taken of guarding against possible overdosage.
(6) The establishment of a reliable guide to dosage control would be a distinct advantage in treatment.

In this connection Dewar suggests that it might prove practicable with further experimentation to use the "Eosinophilic Index" as a guide to specific desensitization—as Spangler has done with the use of venom protein (crotalin) as a *nonspecific* desensitizing agent.

In conclusion, Dewar states three points emerge:

(1) There is a wide field existent for systematic research into the relationship of allergy and epilepsy.
(2) The possibility of sensitization should never be overlooked in the investigation of idiopathic epilepsy.
(3) Investigations as to allergic factors should be undertaken and treatment instituted not only in recent cases, or young subjects, with convulsions, but also in patients who are hospitalized and regarded as chronic.

Dewar's deductions and his several references to my summarized analysis of allergic manifestations in 100 consecutive cases of epilepsy (first series) published in the *Journal of Laboratory and Clinical Medicine*, October, 1927, aroused an urge in me to review my more recent cases of epilepsy in private practice. Since 1908, not including hospital and institutional cases, I have studied and treated 951 epileptic patients with the intramuscular injection of crotalin.

At this time, therefore, I am reporting an analysis of carefully differentiated allergic findings in the patients and ancestors of 205 epileptic cases (75 female and 130 male). The facts contained in the histories of this second series of patients were personally elicited, and a special effort was made to have the patient and relatives make careful inquiry and substantiation of ancestral allergic conditions. Accordingly, I find that I have studied and treated in private practice 229 additional cases of epilepsy since 1927. In this second series a most thorough search was made for allergic findings in both patients and ancestors. Moreover, in the first series, periodic and sick headaches were grouped under the term "Migraine." Headaches in the patients and ancestors in the present series have been divided into "Migraine with Vomiting" and "Periodic, Sick Headaches." The incidence of allergic history in cousins has also been noted and included in summarizing the present series.

Of the 229 cases just reviewed and compiled, two cases proved to be brain tumor, as confirmed by operation; a third was an instance of hyperinsulinism with convulsions, and a chronic decreased sugar tolerance; in the remaining twenty-one cases, a sufficient intelligible history was unobtainable because the patients could not provide data complete enough, for one reason or another, to permit any deductions of significance from an allergic standpoint.

In the present series there remain, therefore, 205 cases on which the data are quite complete, and the summarized abstracted findings in these cases are given in Tables I and II. Clinical allergy is found in 335 instances (Table III) in the ancestors of these 205 epileptic patients, 236 of whom were on the maternal side and ninety-nine on the paternal side. In thirty-four of the 205 patients no allergic conditions in the ancestors

(Text continued on Page 110)

TABLE I. SUMMARY OF ALLERGIC HISTORY OF SEVENTY-FIVE FEMALE EPILEPTICS

Case No.	Age	Married or Single	Order of Birth	Birth—Normal or Instrumental	Breast or Bottle Fed	Convulsions in Infancy	Age Menstruation Established	Age Epilepsy Diagnosed	Allergic Manifestations		Eosinophile (Per cent) Range—with crotalin given intramuscularly
									In Patient	In Ancestors and Family	
1	30	S	4	Nor.	Br.	No	14	19	(Chorea, 12th yr.; petit mal, 14th year). Severe asthma, 22nd year, following influenza	(Sick headaches—Mother and sister) (Convulsions—Maternal aunt and Sister) Hives—Paternal uncle and aunt	9%
x2	18	S	1	Inst.	Bot.	No	12	12	Hives (strawberries)	Hives—Mother and her 4 children (Sick headaches—Mother and maternal grandmother. Asthma—Maternal grandfather Ivy poison—Father	5%
x3	38	M	4	Nor.	Br.	Yes	14	21	Hay fever; hives (Petit mal preceded convulsions)	Migraine with vomiting—Mother and paternal grandmother (Chorea—Sister)	14%
4	15	S	6	Nor.	Br.	Yes	14	15	Eczema; hives; hay fever	Asthma—Mother	10%
x*5	30	M	1	Inst.	Bot.	No	13	20	G.I. upsets. Petit mal, 7th year Ivy poison. Strawberry rash	Hives—Mother (Sick headaches—Maternal grandmother) (Convulsions—Maternal uncle) Ivy poison; hives—Paternal grandfather	7%
x6	21	S	10	Nor.	Br.	Yes	13	12	(Convulsions, 12th year, 6 weeks after scarlet fever) No allergies	Asthma—Mother. (Bilious—Father) (Convulsions—Brother, 8 to 15th year) (Convulsions and asthma—Brother's child)	7%
x*7	45	M	2	Nor.	Br.	No	12	39	Migraine with vomiting— 10 years before convulsions started	Migraine with vomiting—Mother and maternal grandmother Asthma—Maternal grandfather and maternal uncle	5%
x8	53	M	1	Nor.	Br.	No	13	32	Hives; pruritus Purpura hemorrhagica, 32nd year, after which convulsions started	Hay fever—Brother	6%

x9	24	M	3	Nor.	Br.	Yes	13	17	(Convulsions since 17th year, 1 year after birth of 1st child)	Asthma—Maternal grandfather Migraine with vomiting—Mother (Convulsions—Brother)	4%
x*10	27	M	3	Nor.	Br.	No	14	24	(Scarlet fever, 18th year)	Migraine with vomiting—Father	12%
x*11	25	S	2	Nor.	Br.	No	15	15	G.I. upsets, infancy Petit mal, 12th year Migraine with vomiting—14th yr.	Eczema—Maternal uncle Severe migraine—Father and paternal grandmother (Fainting spells—Maternal grandmother)	9%
12	8	S	4	Nor.	Bot.	No	—	7	Ivy poison	None obtainable	8%
13	21	S	1	Nor.	Bot.	No	14	14	No allergies	Migraine with vomiting—Mother	5%
14	42	M	1	Nor.	Br.	No	13	24	G.I. upsets Petit mal, 15th year	Eczema; headaches—Mother (Convulsions—Patient's older sister and maternal aunt)	7%
x15	14	S	1	Nor.	Br.	Yes	11	12	G.I. upsets, 4th to 6th year (Scarlet fever and nephritis, then petit mal, 6th year)	Eczema (Periodic headaches)—Mother	7%
x16	29	S	3	Nor.	Bot.	Yes	13	26	Hives. (Status epilepticus)	Hay fever—Sister (Epilepsy—Paternal grandmother and cousin)	13%
x17	18	S	3	Nor.	Br.	No	13	13	G.I. upsets, infancy	Asthma; hay fever—Maternal aunt Hives—Maternal grandmother (Rickets—Father)	10%
x18	12	S	4	Nor.	Br.	No	12	13	Petit mal, infancy. G.I. upsets (Scarlet fever, 6th year)	Migraine with vomiting—Mother	6%
x*19	23	M	3	Nor.	Br.	No	14	18	(Scarlet fever, 15th year)	(Sick headaches—Mother) (Convulsions—Paternal first cousin)	8%
x*20	36	M	1	Inst.	Br.	No	12	35	Skin tests, negative	None obtainable	6%
x21	14	S	1	Inst.	Br.	Yes	11½	13	(Scarlet fever, 6th year, Petit mal followed)	Hay fever—Mother Periodic headaches—Father Asthma—Paternal grandfather	7%
x*22	18	S	1	Nor.	Br.	Yes	12	13	None	Migraine with vomiting—Mother and maternal grandmother	3%

*Wassermann Negative
xTaking Crotalin and Dilantin.

TABLE I. SUMMARY OF ALLERGIC HISTORY OF SEVENTY-FIVE FEMALE EPILEPTICS—*Continued*

*23	33	M	2	Nor.	Br.	No	14	32	(Periodic headaches since adolescence)	Hives; arthritis—Mother (Convulsions—Father and paternal grandfather)	4%
x*24	23	S	1	Nor.	Br.	No	12	6	G.I. upsets—Headaches and nephritis before convulsions, 6th yr.	Asthma; hay fever—Maternal grandfather	4%
x*25	25	S	1	Nor.	Br.	No	15	15	G.I. upsets—Ivy poison	Ivy poison—Mother (Convulsions—Maternal cousins)	8%
x26	29	S	1	Nor.	Br.	No	13	16	Ivy poison. Headaches at periods before convulsions	Ivy poison—Mother (Periodic headaches—Maternal grandmother)	6%
27	26	M	2	Nor.	Br.	No	12	16	G.I. upsets, infancy	(Convulsions—Brother, sister and maternal aunt)	2%
x28	10	S	2	Nor.	Br.	No	—	9	Eczema, infancy Skin test, negative	Asthma—Maternal uncle Migraine with vomiting—Mother	4%
x*29	26	M	1	Nor.	Br.	No	10	18	Eczema—as a child (Chorea—4th year; round worms, 9th year). Hay fever—21st year	(Convulsions—Maternal first cousin and maternal uncle)	9%
*30	18	S	2	Nor.	Br.	No	12	17	Tobacco sensitivity	Hay fever; hives—Mother G.I. upsets—Father Asthma—Brother	19%
31	32	M	2	Nor.	Br.	No	13	28	None	None obtainable	4%
*32	13	S	2	Nor.	Br.	No	15	9	Hives	Hives—Maternal aunt Asthma—Maternal and paternal grandmothers (Convulsions—Brother, until 5)—Hives	15%
x*33	37	M	2	Nor.	Bot.	No	12	12	Hives	Asthma—Father (Periodic headaches—Sister)	4%
34	27	S	1	Inst.	Bot.	No	14	14	(Scarlet fever, 12th year)	None obtainable	12%
*35	26	M	6	Nor.	Br.	No	13	22	Hives; ivy poison (Petit mal, 19th year) (Sleepwalker)	(Periodic headaches—Maternal grandmother) Eczema; "cat pruritus"—patient's 3-year-old daughter	8%
*36	17	S	1	Nor.	Bot.	No	14	16	G.I. upsets, infancy Hives	Hives—Father and paternal aunt Hay fever—Two maternal aunts Asthma—Paternal aunt	11%

*37	21	S	1	Nor.	Br.	Yes	11	14	Migraine with vomiting. Purpura.	(Convulsions—Father)	13%
38	35	S	5	Nor.	Bot.	No	14	27	None	Hay fever—Sister	7%
*39	22	S	2	Nor.	Bot.	Yes	12	15	G.I. upsets, infancy and childhood	(Convulsions); hives—Father	12%
40	15	S	1	Nor.	Br.	No	15	14	Hives. (Scarlet fever, 7th year, preceded by convulsions)	Migraine with vomiting—Maternal aunt and maternal grandmother (Convulsions—Maternal aunt)	6%
41	36	M	7	Nor.	Br.	No	15	32	(Meningitis, 4th year)	Severe migraine—Mother	6%
42	12	S	7	Nor.	Br.	No	—	6	(Intestinal parasites followed by convulsions, 6th year)	None obtainable	3%
*43	26	S	1	Inst.	Br.	Yes	16	7	(Periodic headaches)	None obtainable	8%
44	6	S	6	Nor.	Br.	No	—	6	Petit mal, 5th year. Hives	Eczema; migraine with vomiting—Mother	10%
45	22	S	2	Nor.	Br.	Yes	14	19	Ivy poison	Hives—Father Hay fever; asthma—Brother	3%
*46	36	S	1	Nor.	Br.	No	13½	14	G.I. upsets. Hay fever Food sensitivity. (Scarlet fever)	Severe migraine—Mother (Periodic headaches—Maternal aunt) (Convulsions—Twin sister, died at 15 months)	7%
47	19	S	3	Nor.	Br.	No	12	19	(Incontinence until 10th year) (Overweight)	None obtainable	10%
48	32	M	2	Nor.	Br.	No	13	31	None	(Periodic headaches—Mother) (Convulsions—Brother) Hives—Sister	10%
49	33	M	7	Nor.	Br.	No	14	25	(Periodic headaches)	(Periodic headaches—Mother)	8%
50	40	M	3	Nor.	Br.	No	14	23	Hives	None obtainable	4%
51	18	S	2	Nor.	Br.	Yes	14	14	(Incontinence until 10th or 12th year). (Chorea, 13th year)	Severe migraine—Mother Asthma; hay fever—Father (Chorea—Brother)	7%
52	16	S	3	Nor.	Br.	Yes	13	13	(Thyroidectomy, 14th year)	None obtainable	8%
53	48	S	3	Nor.	Br.	No	15	8	None	(Periodic headaches—Maternal aunt)	8%

*Wassermann Negative
xTaking Crotalin and Dilantin

TABLE I. SUMMARY OF ALLERGIC HISTORY OF SEVENTY-FIVE FEMALE EPILEPTICS—*Continued*

54	36	M	1	Nor.	Br.	Yes	14	26	None	None obtainable	4%
x*55	33	S	8	Nor.	Br.	No	16	23	Migraine with vomiting—10 years before convulsions started	Eczema—Mother Hives—Two maternal aunts Migraine with vomiting—Maternal aunt (Convulsions—Maternal uncle)	7%
56	39	S	3	Nor.	Br.	No	15	25	None	None obtainable	4%
57	42	M	3	Nor.	Br.	Yes	13	14	Psoriasis (Scarlet fever as a child)	(Periodic headaches—Mother and Two sisters)	7%
58	23	S	1	Nor.	Br.	No	14	17	Hives	None obtainable	4%
59	37	S	5	Nor.	Bot.	Yes	16	29	Migraine with vomiting, 14th year Hives; ivy poison (Scarlet fever, 11th year)	(Periodic headaches—Mother) (Convulsions—Brother, sister and paternal uncle) Hay fever—Sister	13%
60	18	S	2	Nor.	Br.	Yes	14	17	G.I. upsets (Periodic headaches) Hives	(Convulsions—Mother, as child and maternal aunt) Hives—Maternal aunt Migraine with vomiting—Maternal grandmother	6%
61	21	S	1	Inst.	Br.	Yes	13	13	(Petit mal, infancy)	(Headaches—Father and paternal grandfather)	4%
62	3	S	1	Nor.	Bot.	Yes	—	3	G.I. upsets	Hay fever (and headaches)—Mother Hives—Maternal aunt and maternal grandmother Hay fever—Paternal grandmother	8%
63	21	S	1	Nor.	Bot.	No	13	18	G.I. upsets. Ivy poison	Hives (and periodic headaches)—Mother	3%
64	21	S	3	Nor.	Bot.	No	15	20	G.I. upsets	Migraine with vomiting—Mother Hay fever; asthma—Paternal uncle Asthma—Two paternal aunts and paternal grandfather Ivy poison—Brother	2%
65	17	S	2	Nor.	Bot.	Yes	14	15	G.I. upsets. Petit mal, 12th year	Severe migraine—Mother	8%
66	26	S	5	Nor.	Br.	Yes	12	18	None	Hives—Mother. (Spasms in infancy, 4 brothers, 1 sister, none later)	12%

67	20	M	1	Nor.	Br.	No	14	12½	G.I. upsets, infancy (Scarlet fever, 7th year)	Sick headaches—Mother Hay fever—Father Asthma—Paternal uncle	6%
68	33	M	1	Inst.	Br.	Yes	16	25	G.I. upsets, infancy	Eczema (and headaches)—Mother Severe migraine—Maternal uncle and cousin	9%
69	38	M	6	Nor.	Br.	No	18	33	None. (1st convulsions 2 weeks after birth of only child)	(Convulsions—Sister) No allergic history obtainable	2%
70	10	S	1	Nor.	Br.	No	—	9	G.I. upsets; hives	Asthma—Paternal aunt (Convulsions—Paternal uncle)	9%
71	12	S	3	Nor.	Bot.	Yes	11	10	G.I. upsets	Hay fever—Mother and maternal uncle Asthma; eczema—Maternal cousin	3%
72	25	M	2	Nor.	Br.	Yes	14	16	None obtainable	None obtainable	4%
73	7	S	3	Nor.	Br.	Yes	—	7	(Chorea, 6th year)	(Spasm—Mother, when a girl) Hives—Father Spasms, infancy and menopause—Maternal grandmother Severe migraine (Chorea)—Sister	8%
x74	32	M	1	Nor.	Br.	No	15	15	Hives; migraine with vomiting	(Headaches—Father) ("Night spasms"—Paternal aunt)	3%
x75	12	S	8	Nor.	Bot.	No	12	7	Ivy poison	Migraine—Maternal grandmother Hay fever—Paternal uncle Hives—Sister	8%

*Wassermann Negative
xTaking Crotalin and Dilantin

TABLE II. SUMMARY OF THE ALLERGIC HISTORY OF 130 MALE EPILEPTICS

Case No.	Age	Married or Single	Order of Birth	Birth—Normal or Instrumental	Breast or Bottle Fed	Convulsions in Infancy	Age Epilepsy Diagnosed	Allergic Manifestations		Eosinophile (Per cent) Range—with crotalin given intramuscularly
								In Patient	In Ancestors and Family	
x*1	37	S	3	Nor.	Br.	Yes	12	Ivy poison; hay fever	Hay fever—Cousin and maternal aunt (Periodic headaches—Maternal grandmother and aunt). Eczema—Sister	5%
2	13	S	3	Nor.	Br.	Yes	13	(Scarlet fever, 3rd year) (Chorea, 6th year)	(Periodic headaches—Mother) (Neuralgia—Maternal aunt) (Convulsions after scarlet fever—Sister)	19%
x3	24	S	2	Nor.	Br.	No	20	G.I. upsets. (Trolley sickness) Ivy poison	("Sick" headaches—Mother and paternal grandmother)	14%
x*4	15	S	2	Nor.	Br.	No	14	G.I. upsets Ivy poison; hay fever	Hay fever—Father Asthma—Paternal grandmother	26%
x*5	3	S	2	Nor.	Br.	No	3	G.I. upsets	Migraine—(vomiting)—Maternal grandfather (Convulsions—Mother)	15%
x*6	22	S	1	Nor.	Bot.	No	21	(Scarlet fever, 8th year)	None obtainable (orphan)	3%
x*7	40	M	11	Nor.	Br.	No	28	Hives; hay fever	Asthma—Maternal aunt. (Spasms—Brother)	12%
x*8	23	M	7	Nor.	Br.	No	19	Eczema	Eczema (and headaches)—Mother (Convulsions—Oldest sister and paternal aunt)	11%
x9	31	S	4	Nor.	Br.	Yes	3	Periodic severe migraine, between convulsions, started after a fall at age of 2½ years	Eczema—Mother	24%
x10	5	S	2	Nor.	Br.	No	3	G.I. upsets (Marked caries, 1st dentition)	Migraine—Maternal uncle (Convulsions—Father, infancy)	8%
x*11	15	S	1	Nor.	Br.	No	14	G.I. upsets. Skin tests, negative	Migraine—Mother and maternal grandmother	12%
x*12	21	S	1	Nor.	Br.	No	'13	(Petit mal, 5th to 12th year)	Hives—Father	11%

x*13	31	S	2	Nor.	Br.	No	25	G.I. upsets, periodically	Hay fever—Brother (Headaches—Mother) (Psychosis—Younger brother)	6%
x*14	15	S	4	Nor.	Bot.	No	11	G.I. upsets, infancy	Asthma—Father. (Convulsions—Paternal aunt)	5%
x*15	6	S	10	Nor.	Bot.	Yes	5	G.I. upsets	None obtainable	7%
x*16	55	M	5	Nor.	Br.	No	51	Hives; hay fever (Scarlet fever as a child)	Migraine—Sister	7%
17	27	S	2	Nor.	Br.	No	21	Eczema (Skin tests, negative)	Asthma—Father Hives—Brother. (Convulsions—Paternal uncle)	7%
x18	8	S	2	Nor.	Bot.	Yes	7	G.I. upsets; Hives (Petit mal, 6th year)	Migraine—Mother. Hives—Father and 2 brothers Asthma—Oldest brother and maternal and paternal uncles. Hay fever—Youngest brother	5%
x19	14	S	3	Nor.	Br.	Yes	10	(Petit mal, 9th year)	No allergic history obtainable	7%
20	21	S	3	Nor.	Bot.	No	8	Eczema, 1st year	Hives—Brother (Periodic headaches—Mother and maternal grandmother)	6%
21	29	S	1	Inst.	Bot.	Yes	20	No allergies	Asthma—Mother, maternal grandmother and maternal aunt Migraine—Mother	2%
22	12	S	1	Inst.	Bot.	Yes	4	G.I. upsets. (Convulsions before scarlet fever at 2 years) (Skin test, negative)	("Sick" headaches—Mother)	4%
*23	38	M	1	Nor.	Br.	No	27	Eczema—since 16th year Migraine—before convulsions started	Asthma—Maternal cousin Eczema—2 Brothers ("Sick" headaches—Mother)	15%
*24	10	S	1	Nor.	Bot.	Yes	7	G.I. upsets, infancy (Skin tests, negative)	Migraine—Mother Eczema—Maternal aunt Hives—Brother (Convulsions—Maternal grandmother)	7%
25	18	S	1	Nor.	Br.	No	11	(Periodic headaches) (Skin tests, negative)	Hives—Mother	3%

*Wassermann Negative.
xTaking Crotalin and Dilantin.

TABLE II. SUMMARY OF THE ALLERGIC HISTORY OF 130 MALE EPILEPTICS—*Continued*

26	16	S	1	Inst.	Bot.	No	12	Severe migraine, early childhood	(G.I. upsets; periodic vomiting—Mother)	4%
27	24	S	3	Nor.	Br.	No	23	Hives	("Sick" headaches—Brother)	10%
28	18	S	2	Nor.	Br.	Yes	16	(Intestinal parasites)	Migraine—Mother, father and paternal grandmother (Convulsions—Paternal aunt)	9%
29	38	M	1	Nor.	Bot.	Yes	33	(Subject to convulsions until 5th year—then none until 33rd year. Sleepwalker until puberty)	Severe migraine—Brother G.I. upsets, migraine (and psoriasis)—Sister Hives; ivy poison (and chorea)—Son	11%
30	28	S	1	Inst.	Bot.	Yes	10	(Trephined)—15th year	Asthma—Father and paternal cousin (Headaches—Mother, maternal grandmother and uncle) (Chorea—Sister)	8%
31	11	S	1	Inst.	Bot.	No	10	G.I. upsets. Eczema, infancy Migraine, 8th year; scarlet fever, 9th year. (Skin tests, negative)	Hives—Mother. Migraine—Father Asthma—Maternal grandmother Asthma; Hay fever—Maternal grandfather	16%
32	33	S	1	Inst.	Br.	No	5	(Scarlet fever, 8th year)	Hives—Mother. Eczema—Brother Migraine—Paternal aunt (Convulsions—Paternal grandfather and aunt) (Shingles—Father)	6%
33	26	M	5	Nor.	Br.	No	16	Hay fever	Severe migraine—Father	13%
34	25	S	1	Nor.	Br.	No	14	None	None obtainable	10%
x*35	32	M	1	Nor.	Br.	No	31	G.I. upsets Eczema; hives	Asthma—Maternal aunt ("Sick" headaches—Mother)	9%
36	22	S	1	Nor.	Bot.	Yes	15	G.I. upsets. Ivy poison (Rickets) (Scarlet fever, 7th year)	Hives—Mother. Migraine—Father Asthma; hives—Maternal grandmother (Convulsions—Maternal aunt)	15%
37	62	M	1	Nor.	Br.	Yes	60	G.I. upsets (Scarlet fever, 21st yr.) (Herpes zoster, 56th year)	(Pulmonary tuberculosis—Mother)	7%
38	13	S	1	Inst.	Bot.	No	12	G.I. upsets	None obtainable	7%
39	3	S	1	Inst.	Bot.	Yes	1	Eczema; hives	Asthma—Maternal uncle and paternal aunt Hives—Father. (Headaches—Mother)	12%

40	24	S	2	Nor.	Br.	No	24	Hives. (Petit mal, 23rd year) (Uncinariasis, 24th year)	Migraine (and convulsions)—Mother Hives—Brother	26%
x*41	45	M	5	Nor.	Br.	No	44	None	Severe migraine—Mother	9%
42	12	S	1	Nor.	Bot.	No	11	Periodic G.I. upsets—before convulsions	Asthma—Maternal grandfather and maternal cousin Hives; hay fever—Paternal grandfather	6%
*43	27	S	10	Nor.	Br.	Yes	22	None	Hives—Mother and sister Asthma—Maternal grandmother and maternal aunt Hay fever—Sister and maternal aunt	11%
x*44	25	S	3	Nor.	Bot.	Yes	24	G.I. upsets. Ivy poison	Hives; ivy poison—Mother Eczema—Maternal grandmother Peptic ulcer—Father	8%
45	23	M	3	Nor.	Br.	No	17	No allergies	Asthma—Maternal grandfather. (Headaches—Mother) Ivy poison; hives (and convulsions)—Sister	6%
*46	10	S	1	Inst.	Bot.	Yes	6	G.I. upsets	Asthma—Paternal grandfather (Periodic headaches—Father)	9%
*47	22	S	4	Nor.	Br.	No	11	None	Hives—Father. (Headaches—Mother) (Convulsions—Paternal uncle)	7%
*48	19	S	3	Nor.	Bot.	Yes	11	G.I. upsets, infancy	("Sick" headaches—Mother)	5%
49	15	S	1	Inst.	Bot.	No	9	G.I. upsets, through childhood	Eczema; ivy poison ("spells" when young)—Mother "Bilious" attacks—Father (Convulsions—Maternal uncle)	
50	8	S	2	Nor.	Br.	No	7	(Petit mal, infancy)	(Convulsions—Paternal cousin)	7%
51	14	S	1	Inst.	Bot.	No	14	(Scarlet fever)	Hives (and "sick" headaches)—Mother Asthma—Paternal grandfather	7%
52	10	S	6	Nor.	Br.	Yes	7½	None	None obtainable	12%
53	31	M	1	Nor.	Br.	No	14	Ivy poison	(Convulsions—Mother)	7%
54	44	M	2	Nor.	Br.	No	16	Hay fever	(Convulsions—Brother)	10%
55	16	S	4	Nor.	Br.	No	16	None	Hives—Paternal aunt (Periodic headaches and convulsions—Father)	6%

*Wassermann Negative.
xTaking Crotalin and Dilantin.

TABLE II. SUMMARY OF THE ALLERGIC HISTORY OF 130 MALE EPILEPTICS—*Continued*

56	27	M	5	Nor.	Br.	No	19	Hay fever	No allergic history obtainable	8%
*57	7	S	2	Nor.	Br.	Yes	7	G.I. upsets Angioneurotic edema	Periodic G.I. upsets—Mother Hives; dermagraphia—Father Asthma—Maternal and paternal grandmothers Asthma; angioneurotic edema—Brother	11%
58	25	S	5	Nor.	Br.	Yes	14	No allergic history	Asthma—Maternal uncle	13%
59	28	M	2	Nor.	Br.	No	20	Ivy poison	None obtainable	6%
60	10	S	1	Nor.	Bot.	Yes	9	G.I. upsets (Scarlet fever, 8th year)	Eczema; migraine—Maternal grandmother Hives—Maternal grandfather. Hay fever—Maternal aunt Asthma (and convulsions when young)—Father (Convulsions—2 brothers and 1 sister, died)	9%
*61	4	S	1	Nor.	Br.	Yes	4	Spasms, 3rd year No allergic history	Migraine—Mother	20%
62	18	S	3	Nor.	Br.	No	13	None	(Chorea—Sister) (Headaches—Mother)	6%
63	31	S	4	Nor.	Br.	Yes	28	None	(Convulsions—Adult brother)	7%
64	14	S	1	Inst.	Bot.	No	10	G.I. upsets	Eczema—Father. Hives—Maternal aunt	5%
65	17	S	1	Nor.	Br.	Yes	14	Eczema	Asthma—Maternal grandmother. (Headaches—Mother)	8%
66	19	S	2	Nor.	Bot.	No	9	No allergies	(Periodic headaches—Mother)	5%
*67	17	S	1	Caes.	Br.	No	6	Severe migraine, recently	Severe migraine—Mother Asthma—Maternal and paternal grandfathers	7%
*68	10	S	2	Nor.	Bot.	Yes	6	G.I. upsets (Petit mal)	Ivy poison; "bilious" attacks—Father (Convulsions—Maternal grandfather)	10%
69	17	S	3	Nor.	Br.	No	12	(Headaches following fall, 11th yr.)	(Convulsions—Paternal uncle) Pruritus; food sensitivity—Paternal grandmother	10%
70	28	S	7	Inst.	Br.	No	17	No allergies	Migraine—Mother and maternal aunt Hives—Brother	6%

*71	22	S	2	Nor.	Bot.	Yes	10	G.I. upsets. (Condensed milk after 1st month)	Asthma; hives—Maternal grandfather Asthma—Paternal grandfather. Migraine—Paternal aunt	6%
72	3	S	1	Inst.	Br.	No	3	None	Asthma—Paternal grandfather ("Sick" headaches—Father)	9%
73	28	S	5	Nor.	Br.	No	18	(Scarlet fever, 5th year)	(Convulsions—Paternal uncle)	7%
74	14	S	8	Nor.	Br.	No	6	(Status at 8th year)	("Sick" headaches—Mother and maternal grandmother	14%
75	23	S	5	Nor.	Br.	No	13	No allergic history	None obtainable	7%
*76	12	S	2	Nor.	Bot.	Yes	8	G.I. upsets, as a baby	Eczema (and periodic headaches)—Mother Eczema—Maternal grandmother. (Convulsions—Paternal aunt)	17%
77	28	S	1	Nor.	Br.	Yes	10	(Food tests, negative)	Asthma; eczema; hives; hay fever—Paternal grandmother. (Convulsions—Maternal aunt)	3%
78	36	M	1	Nor.	Bot.	No	14	Asthma, as a boy, before epilepsy, then stopped. Hives	None obtainable	12%
79	14	S	1	Inst.	Bot.	No	11	G.I. upsets, in infancy Hives	("Sick" headaches—Mother). Eczema—Maternal grandmother. Ivy poison—Father. Hives—Sister	6%
80	30	M	2	Nor.	Bot.	Yes	12	G.I. upsets (Chorea—Childhood)	("Sick" headaches—Mother) (Convulsions—Younger brother)	6%
*81	29	M	2	Nor.	Br.	No	28	No allergic history	(Convulsions—Father) Severe migraine—Sister	8%
82	53	M	1	Nor.	Br.	No	50	G.I. upsets (Scarlet fever, as boy)	Hives; food sensitivity—Mother Hives—Father and paternal uncle (Periodic headaches—Maternal grandmother)	5%
83	45	M	2	Nor.	Br.	No	40	G.I. upsets with headaches (Scarlet fever, as boy)	Hives—Mother Asthma—Maternal grandmother	4%
*84	25	M	1	Nor.	Br.	No	24	None	Migraine—Mother. Asthma—Paternal grandmother and brother	8%

*Wassermann Negative.
xTaking Crotalin and Dilantin.

TABLE II. SUMMARY OF THE ALLERGIC HISTORY OF 130 MALE EPILEPTICS—*Continued*

x*85	15	S	2	Inst.	Bot.	Yes	15	G.I. upsets	Ivy poison—Mother and father Migraine—Maternal grandmother	7%
86	22	S	1	Nor.	Br.	No	14	G.I. upsets Migraine until 13th year	(Periodic headaches—Mother, father and maternal grandmother) Migraine—Paternal aunt	3%
*87	27	S	4	Inst.	Br.	No	16	G.I. upsets (Scarlet fever)	Eczema—Mother Asthma; hives—Maternal grandmother	5%
x88	29	S	6	Nor.	Bot.	No	21	G.I. upsets (Typhoid fever, 17th year)	Migraine—Mother and sister	8%
*89	31	S	2	Nor.	Br.	No	23	G.I. upsets Severe migraine; eczema	Eczema—Mother ("Sick" headaches—Father and maternal aunt) Asthma—Brother. Hives—Another brother	13%
90	12	S	1	Inst.	Bot.	No	11	G.I. upsets	Migraine—Mother and maternal grandmother Hives—Maternal aunt Asthma; hay fever—Maternal cousin Hay fever—Paternal grandmother	2%
91	12	S	1	Nor.	Bot.	Yes	3	G.I. upsets (Status for 6 hours, 9th year)	Ivy poison; migraine—Father Asthma—Paternal grandmother. Hives—Maternal grandmother. (Convulsions—Paternal uncle) (Chorea—Sister)	14%
*92	20	S	6	Nor.	Br.	No	16	(Scarlet fever, 5th year)	None obtainable	16%
93	9	S	1	Inst.	Bot.	Yes	4	G.I. upsets (Scarlet fever)	Severe migraine—Both parents and maternal grandmother	3%
94	21	S	1	Nor.	Bot.	Yes	14	G.I. upsets (Scarlet fever) Hives; ivy poison	Eczema—Paternal grandmother and brother	6%
95	16	S	1	Nor.	Br.	Yes	16	No allergies	Hay fever—Mother. (Headaches—Maternal aunt) Hives—Paternal aunt	10%
*96	43	M	1	Nor.	Br.	No	40	None	(Convulsions—Mother)	10%
x*97	19	S	4	Nor.	Br.	Yes	11	Eczema	Eczema—Sister. (Convulsions—Father)	2%
98	17	S	1	Nor.	Br.	No	17	G.I. upsets. Hives, 3rd year Asthma, 5th year. (Scarlet fever, 16th yr.)	(Periodic headaches—Mother) Migraine—Maternal grandmother. Hay fever—Maternal aunt	7%

99	11	S	1	Inst.	Br.	Yes	6	G.I. upsets. Ivy poison	Severe migraine—Mother	7%
100	24	S	1	Nor.	Br.	Yes	20	None	Asthma—Father. (Headaches—Mother)	5%
101	48	S	4	Nor.	Br.	No	43	Eczema; pruritus Severe migraine for 20 years	None known	11%
*102	52	M	2	Nor.	Bot.	No	44	(Chorea, 12th year)	None obtainable	5%
x*103	21	S	3	Nor.	Br.	No	20	Hives (Nocturnal incontinence until 10)	Asthma—Mother	9%
104	22	S	8	Nor.	Br.	Yes	14	None	None obtainable	8%
105	46	M	1	Nor.	Br.	No	43	Hives; eczema (Scarlet fever)	None known	6%
106	49	M	7	Nor.	Br.	No	45	Severe migraine, as young man	Asthma—Mother. (Headaches—Father) (Convulsions—2 Brothers)	8%
107	26	S	1	Nor.	Br.	No	21	("Fainting spells" started at 5th year)	("Sick" headaches—Mother) ("Fainting spells"—Father)	9%
*108	28	S	4	Nor.	Br.	Yes	24	None	Asthma—Mother	6%
109	11	S	4	Nor.	Br.	No	10	G.I. upsets. (Egg sensitivity) Eczema (and petit mal)	("Sick" headaches—Mother and 2 paternal aunts)	16%
110	19	S	2	Nor.	Br.	No	17	G.I. upsets. Hives (Scarlet fever, 2nd year) (Petit mal, 12th year)	Asthma; hives—Mother Asthma—Maternal grandfather. Migraine—Maternal aunt. Hives—Brother	14%
*111	16	S	1	Inst.	Bot.	Yes	13	G.I. upsets, infancy	("Sick" headaches—Mother and maternal aunt) Asthma—Paternal aunt and younger sister	9%
112	22	S	1	Nor.	Br.	No	17	None	No allergic history obtainable	6%
113	19	S	1	Nor.	Br.	No	12	(Scarlet fever, 5th year)	Severe migraine—Mother (Psychosis—Maternal aunt)	4%
114	20	S	2	Nor.	Bot.	No	13	G.I. upsets, infancy (Scarlet fever, 8th year)	Hives—Mother ("Fainting spells"—Paternal aunt)	13%
115	24	M	2	Nor.	Br.	No	14	(Scarler fever, as child)	Asthma—Paternal uncle	7%

*Wassermann Negative.
xTaking Crotalin and Dilantin.

TABLE II. SUMMARY OF THE ALLERGIC HISTORY OF 130 MALE EPILEPTICS—*Continued*

116	7	S	4	Nor.	Br.	No	7	None (1st convulsion 2 weeks after appendectomy, 7th year)	(Headaches—Mother). (Pemphigus—Father)	7%
117	11	S	1	Inst.	Bot.	Yes	11	G.I. upsets. Ivy poison (Convulsions with pneumonia, 4th year)	(Convulsions; G.I. upsets—Father, as child) Migraine—Maternal grandmother. Asthma—Maternal cousin. (Convulsions, infancy—Younger sister)	18%
118	21	S	2	Inst.	Bot.	Yes	13	G.I. upsets, infancy	Migraine—Mother and maternal grandmother Ivy poison; hives—Father Hives—Paternal grandmother	10%
119	37	M	2	Nor.	Br.	No	14	(Sleepwalker as child)	None obtainable	6%
120	18	S	4	Nor.	Bot.	No	6	(Petit mal, 5th year)	Asthma—Maternal grandfather. Hay fever—Maternal cousin	2%
121	17	S	1	Inst.	Br.	No	13	None	Migraine—Mother and maternal aunts Hives—Maternal grandmother. G.I. upsets—Father	7%
x*122	10	S	1	Nor.	Bot.	Yes	6	Skin tests, negative (Scarlet fever, 2nd year) (Burned at 2½ years then spasms)	No allergic history	14%
123	1	S	3	Inst.	Bot.	Yes	1	G.I. upsets	Hives (and "sick" headaches)—Mother (Convulsions—Maternal aunt)	5%
124	21	S	3	Nor.	Bot.	No	16	None	("Sick" headaches—Mother) (Convulsions—Maternal cousin) Asthma—Paternal grandfather	4%
*125	50	M	4	Nor.	Br.	No	48	Pruritus (and headaches periodically)	None obtainable	7%
126	12	S	8	Nor.	Br.	No	6	None	Asthma for years—stopped (then "sick" headaches) —Mother (Convulsions—Sister, in infancy)	14%
127	24	S	4	Nor.	Br.	Yes	15	(Incontinence, 9th to 12th year)	Migraine—Mother Hives—Maternal aunt ("Sick" headaches—Father and sister)	5%

128	20	S	2	Nor.	Br.	No	14	Skin tests, negative No allergies	Severe migraine—Maternal aunt and cousin	4%
129	7	S	1	Nor.	Br.	Yes	4	(Convulsions, 9th month, after eating 1st egg. Subsequent egg sensitivity)	Migraine—Mother Asthma—Paternal grandfather (Convulsions—Paternal uncle)	8%
130	18	S	1	Inst.	Bot.	No	10	G.I. upsets Supra-orbital headaches Leukopenic index, positive for milk and egg Skin tests, negative (Scarlet fever, 4th year)	Asthma—Paternal uncle and paternal cousin Hay fever—Another paternal uncle Migraine—Maternal aunt	8%

*Wassermann Negative.
xTaking Crotalin and Dilantin

TABLE III. HEREDITARY DEDUCTIONS FROM TABLES I AND II

Summary of Clinical Allergic Symptoms in the Patient, and Hereditary Manifestations in the Immediate Ancestors of 205 Epileptic Patients (75 Female and 130 Male), Studied in Private Practice

Allergic Manifestations	Patients	Brothers	Sisters	Maternal						Paternal						Total Number Ancestors Showing Allergic Manifestations
				Mother	Grandmother	Grandfather	Aunts	Uncles	Cousins	Father	Grandmother	Grandfather	Aunts	Uncles	Cousins	
Hay Fever	10	4	5	6		2	7	1	2	3	3	1		2		27
Asthma	3	7	1	8	9	10	6	5	5	6	5	9	5	4	1	73
Hives (Pruritus)	33	11	6	18	4	3	8			11	2	3	3	1		53
Eczema	13	4	2	11	3	1	1	1	2	3	2					24
Migraine with Vomiting	11	1	5	30	13	2	4	2		5		1	3			60
*Periodic Sick Headache	12	1	3	47	10	1	7	1	1	12	2	2	2			85
Ivy Poison	18	3	1	5						4		1	3			13
Totals	100	31	23	125	39	19	33	10	10	44	14	17	13	10	1	335
			54			236						99				
Convulsive Seizures (22 of these also had Petit mal)	205	11	10	8	2	1	5	4	7	10	1	2	9	7	3	59
			21			27						32				

*In the ancestors and patients with periodic sick headaches and convulsive seizures, allergy can only be postulated.

were elicited. One hundred instances of allergy occurred in the patients themselves. Thirty-six of the 205 patients gave a history of having had scarlet fever. It is of interest to note that among the brothers and sisters of the patients there were fifty-four cases showing one or another form of allergy.

Among these 205 patients with convulsive seizures, twenty-two of them also had petit mal; twenty-one of these patients' brothers and sisters were subject to convulsions; and there was a history of convulsive seizures among fifty-nine of the immediate ancestors, twenty-seven on the maternal side and thirty-two on the paternal side (Table III). Other summarized deductions are given in Table IV.

Until a definite test for allergy is established, it can only be postulated that convulsive seizures are allergic in nature, even when the patient has shown one or more forms of allergy, or in whose immediate ancestors allergy has occurred.

In the present series of 205 cases, sixty-two blood Wassermann tests

were negative; in the remaining 143 no Wassermann tests were made as there was no clinical suspicion or history of lues.

TABLE IV. SUMMARIZED DEDUCTIONS OF TABLES I AND II.

130 Males, 29 married. 75 Females, 26 married.

Age Epilepsy Diagnosed (grouped in decades)

First to ninth year inclusive	36	17.5 per cent
Tenth to nineteenth year inclusive	107	52.1 per cent
Twentieth to twenty-ninth year inclusive	39	19.0 per cent
Thirtieth to thirty-ninth year inclusive	9	4.4 per cent
Fortieth to forty-ninth year inclusive	9	4.4 per cent
Fiftieth to fifty-ninth year inclusive	4	1.4 per cent
Sixtieth to sixty-ninth year inclusive	1	0.5 per cent

82 First born	48 Breast fed, 6 convulsions in infancy	12.5 per cent
	34 Bottle fed, 20 convulsions in infancy	58.8 per cent
30 Instrumentally delivered	11 Breast fed, 5 convulsions in infancy	45.4 per cent
	19 Bottle fed, 10 convulsions in infancy	52.6 per cent

Bottle feeding (protein sensitivity to milk or food foreign to the mother) may be a more potent factor in the development of infant convulsions than a difficult or instrumental birth.

48 patients Breast Fed, 6 had convulsions in infancy, or....12.5 per cent
34 patients Bottle Fed, 20 had convulsions in infancy, or....58.8 per cent

Gastro-intestinal hypersensitivity to cow's milk or other substitute for mother's milk appears to be a decided factor in the development of infant convulsions in the atopic child.

Since dilantin sodium became available in 1938, in this series of 205 patients forty-seven have been taking dilantin in various doses ranging from 3 to 6 grains daily, while weekly injections of crotalin were being given intramuscularly. Thirteen of these patients had been taking dilantin for various periods of time before crotalin was started; seventeen had received injections of crotalin before any dilantin was administered; while seventeen were started on dilantin and crotalin at the same time. The therapeutic effect of crotalin alone, or with dilantin, will not be discussed at this time except to state that about 60 per cent of the patients on the combined treatment did better than when taking either form of therapy alone. Of this series 158 have never taken any dilatin.

The side effects from the administration of dilantin have not been numerous: two of the patients, while taking dilantin, developed status epilepticus, neither of whom had previously suffered a status, and one of whom died; there were two with psychotic behavior symptoms, and one developed a marked apprehensive state. Skin symptoms included one with a scarletina-like rash with fever, and one with a similar rash without fever, and one with a marked impetigo-like eruption. The digestive disturbances included two cases of rather severe gastric crises; six had more-or-less vague digestive disturbances; six developed marked hyperplasia of gums, and nine a moderate hyperplasia.

The last column in Tables I and II tabulate the eosinophile percentage

range in the differential leukocyte count when crotalin injections were being administered.

TABLE V. PERCENTAGE RANGE OF EOSINOPHILE CELLS IN THE DIFFERENTIAL BLOOD COUNTS OF 205 EPILEPTIC PATIENTS RECEIVING VENOM PROTEIN (CROTALIN) INJECTIONS INTRAMUSCULARLY.

No. Cases	*Per Cent Eosinophiles*
1	26
—	25
1	24
—	23
—	22
—	21
1	20
2	19
1	18
1	17
3	16
4	15
8	14
7	13
9	12
7	11
12	10
15	9
22	8
34	7
26	6
14	5
18	4
13	3
6	2
—	1

It has been the writer's experience that the best results are obtained from crotalin when an eosinophilic response averaging 7 per cent or more is obtained. This rise in eosinophiles (eosinophilic index) has been used to determine strength of dose and frequency of injections. In view of the recent report of Mansell[19] in the London *Lancet* for January 2, 1943, on "Crossed Desensitization in Allergic Diseases," evidence would seem to show the possibility that nonspecific desensitization with crotalin may alter the immunologic cellular mechanism in the epileptic individual and thus account for the beneficial results secured.

COMMENT

While cutaneous testing is a recognized procedure in the investigation of the etiologic factors in most conditions regarded as allergic, a skin reaction is not the necessary sine quo non criterion of the allergic state. Disturbances in the physical and chemical mechanisms of the blood and tissues (biological changes in the soil) are more and more being considered fundamentally responsible for alterations in cellular activities, which are important factors in allergic hypersensitivity. Accordingly, to depend on negative skin reactions to decide absence of an allergic state is not always infallible.

That recognized allergic symptoms may appear in a patient afflicted with epilepsy is a well-established fact, but whether a convulsion is directly or indirectly indicative of a patient's *lack* of development of an allergic cellular mechanism of defense needs immunologic proof.

It seems at least reasonable to assume, however, that in a patient who suffers periodic states of unconsciousness, with or without convulsive seizures, and who has a familial allergic background with some definitely recognized personal hypersensitivity manifestation, there is the possibility of allergy being an etiologic factor, which is well worth while investigating.

Finally, nonspecific desensitization with intramuscular injections of venom protein (crotalin) in doses varying from 1/400th to 1/50th grain has the effect of beneficially altering a patient's internal environment (soil) and acts as an adjuvant to anticonvulsive medication.

COMENTARIO

El experimento cutáneo es un procedimiento reconocido en la investigación de los factores etiológicos y se considera como alérgico en casi todas las condiciones, la reacción del dérmis no es lo necesario del "sine quo non criterion" del estado alérgico. El desorden en mecanismos físicos y químicos de la sangre y de los tejidos se consideran fundamentalmente mucho más responsables por sus cambios en las actividades celulares, los cuales son factores de gran importancia en la hipersensibilidad alérgica. En efecto, el depender que las reacciones negatives del dérmis y el decidir que hay ausencia de un estado alérgico no es siempre infalible. Es un hecho bien reconocido que los síntomas de alergia pueden manifestarse en un paciente que sufre epilepsia, pero si una convulsion es directa o indirectamente el resultado de una falta de desarrallo del paciente de una reacción de defensa, requiere prueba de procedimientos inmunológicos. Sin embargo, parece ser razonable el asumir; que un paciente que esté en un estado periódico de insensibilidad con o sin convulsiones acogidas, y quien tenga una historia hereditaria de alergia manifestación personal de hipersensibilidad definidamente reconocida; hay la posibilidad de alergia siendo un factor etiológico, el cual vale la pena de investigarlo. Finalmente, la desensitización no específica con las inyecciones intramusculares de crotalin en dósis que varían de una fracción de 1/400 a 1/50 en grs. tiene el efecto de alterar benéficamente el sístema interior de un paciente y obra como un auxiliar a la medicación anticonvulsiva.

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FLEA BITE ALLERGIES ARE RELIEVED BY VACCINE

Successful vaccination against the hives and asthma some people get from flea bites has been achieved by a flea antigen developed at the University of California, Dr. Barbara C. McIvor and Dr. L. S. Cherney of the University Medical School announced.

Fleas are a serious threat to health because they may carry the germs of typhus fever and plague. The flea antigen is not directed against this danger, but to the severe reactions some people have from bites of non-infected fleas.

In California, North Africa and probably other parts of the world the flea is a pest aside from its disease-carrying danger, just as mosquitoes are. In such regions the antigen should prove a boon to hypersensitive persons.

In the University investigations 115 out of 128 patients were relieved of symptoms by the vaccination. Three failed to complete the course of treatments. Trials by forty-one doctors in other parts of the country showed that all but five of ninety-two patients were helped.—*Science News Letter*, September 25, 1943.

TEMPOROMANDIBULAR ARTHROPATHY IN SERUM SICKNESS

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WHILE the symptom complex to which we give the name of serum sickness has been known since Dennis first transfused lambs' blood into human beings in 1667, it remained a medical curiosity until Behring introduced the antitoxin treatment of diphtheria in 1890. At first the untoward symptoms occasionally following the injection of Behring's serum were blamed on the antitoxin element in the serum. The next year, however, Johannessen, by obtaining the same symptoms by the injection of normal horse serum, proved that the condition was caused by the injection of the serum of an incompatible animal.

During the early years of the use of antitoxin the attacks of serum disease were so rare and so infrequently followed by fatal results, and the benefits of serum therapy were so tremendous, that it was customary to pay little attention to the possibility of its occurrence and to accept it as a small evil to be met in the production of an enormous amount of good.

Following Theobald Smith's discovery of anaphylaxis and the introduction of diphtheria toxin-antitoxin as a routine prophylactic measure, however, the picture changed. For many years the great majority of children were given these prophylactic inoculations and a very considerable number of them, as a result, have become hypersensitive to horse serum, and, while the procedure has wiped diphtheria from the map and made the use of diptheria antitoxin a rare procedure, it has added greatly to the danger of the use of all other sera.

While the use of tetanus antitoxin is indicated in all cases of punctured wounds, unless the patient is suspected of being a case of horse allergy, it must be used with discretion, and symptoms arising thereafter must be observed with care and properly interpreted.

When a patient has had no previous dose of horse serum the symptoms of serum sickness usually occur between eight and twelve days after the injection. These are fever, urticaria, edema and pains and stiffness in the joints. When the patient has been sensitized by a previous dose of serum the reaction may be immediate urticaria, collapse, and, unless adrenalin is administered promptly, death may result.

The diagnosis of the condition is usually quite simple, and the problem is one of prompt therapy. There is one symptom of serum sickness which, when coming on following an injection of tetanus antitoxin, requires careful differential diagnosis, as upon the correct interpretation of the symptom may depend the patient's life. This is the occurrence of temporomandibular anthropathy.

The condition and its difficulties are well illustrated in the following cases:

Case 1.—F. P., a white garage worker, twenty-five years of age, was seen first by one of us (PLT) in the emergency room at St. Elizabeth Hospital, Utica, on February 8, 1938. Examination of his previous history showed no signs of allergy. There was no history of asthma, hay fever or eczema. As a child he had scarlet fever, chicken pox and pertussis. He received inoculations against diphtheria but was unable to state the number of injections. He probably received toxin-antitoxin as the toxoid was not used at that time. He had pneumonia and states he received six inoculations for it. Presumably this was vaccine because at this time the serum treatment of pneumonia was not in common use. In 1932 he had an attack of what he termed "stomach trouble," and states that since that time he has had occasional fainting spells with feeling of oppression in the chest. He has also been more susceptible to small local skin infections. His operative history consisted of an appendectomy and a thoracentesis following pneumonia. His habits were regular, appetite good, and he had no constipation. He had had no genito-urinary disease. He had had one attack of urticaria several years ago. He stated that he had frequently been near horses and never had the slightest difficulty in breathing, or had he given a history of any allergic manifestations. Twice prior to the present condition he had received 1,500 units of tetanus antitoxin as treatment for grossly contaminated wounds received in his occupation. They were not followed by any reaction.

Present Illness.—While lying under a car on a small movable truck, a pencil which was in his pocket slipped out and remained standing, point up, between the slats of the truck. On dropping his head backward the sharp end of the pencil was driven into the scalp and a piece of graphite broke off and remained in the wound. He was taken to the hospital and given 1,500 units of tetanus antitoxin. The scalp was opened, the graphite removed and three dermal sutures were inserted. Drainage was maintained by a rubber dam drain through the lower angle. The wound healed without difficulty; no infection occurred. Ten days later the patient returned to the hospital complaining of shortness of breath, intense itching of the skin, swelling of the face and inability to open the jaw completely.

Physical Examination.—The patient was a well-developed and well-nourished white man, somewhat overweight. The face was very puffy and somewhat engorged. The eyes were bloodshot and any effort to open the lower jaw completely was unavailing. The masseter reflex was not exaggerated. There were no convulsions. The patient was perfectly lucid though appprehensive about his jaw, and complained of general itching. The pupils reacted to light and accommodation. There was no nystagmus. The conjunctivæ were somewhat suffused. The tongue was moist and slightly coated. Inspection of the pharynx was impossible because of inability to open the jaw. In the posterior region of the right side of the scalp there was a healed scar of recent date. This scar was movable on the bone. There was no tenderness or swelling. The entire face was swollen particularly about the lips. The neck showed very marked urticaria, some of the wheals being 8 to 10 cm. across. Chest auscultation showed occasional rales but no asthmatic sounds. The percussion note was resonant throughout. The heart sounds were loud and booming. There was no enlargement of either side of the heart and no murmurs were heard. The abdomen showed a generalized urticaria. No tumor masses or tenderness was made out. The liver, spleen and kidneys were not palpable. The genitalia showed nothing abnormal except swelling of the scrotum. The knee jerks were normal. Babinski test was negative. The skin showed a generalized urticarial rash more marked over the chest, abdomen and axilla with extension down the arms and legs.

This case presented the picture of a severe serum reaction and would have been of no great interest were it not for the rigidity of the jaw which raised the question. Had this man been insufficiently treated for tetanus which was beginning to manifest itself in masseter spasm, or was the entire picture simply due to a highly allergic reaction to the injection of tetanus antitoxin about ten days before? The rigidity of the jaw was constant, there was no increased reflex of the masseter muscles. There seemed to be some weakness in the muscles of the forearm and some retardation of movements of the brow and upper lids. The patient was seen in consultation both with another surgeon and with an allergist. The surgeon examined the patient and diagnosed the condition as one of insufficiently treated tetanus and advised the immediate use of large doses of tentanus antitoxin as the only way to prevent a mortality. Since, at this time there was no dyspnea, the arms were covered with large wheals and the patient complained of intense itching, it did not seem justifiable to give him any more tetanus antitoxin. He was given adrenalin which produced very little result, and an attempt was made to desensitize him. One drop of antitoxin diluted one hundred times was injected in the skin and immediately an urticarial wheal developed. In the meantime, the rigidity of the jaw lessened. The patient was seen the same afternoon in consultation by one of us (TWC), who diagnosed the case as one of severe serum reaction. The consultation note was as follows: "In consideration of the patient's great hypersensitivity to horse serum and in view of the two facts that the symptoms suggesting tetanus are moderating, and that cephalic tetanus, that produced by a wound on the head, has an outlook far better than other types of tetanus, I believe that the danger of anaphylactic death if more serum is given is far greater than that of any symptoms of tetanus which may develop. I advise against the further use of serum and suggest that the allergic condition be treated with adrenalin as is being done."

The next day the urticaria was better, the itching was much less severe and the patient could open the jaw to the full extent. In four days he was discharged as cured.

Comment.—The interest point in this case was the likelihood of being alarmed at the appearance of jaw rigidity and of incorrectly diagnosing the condition and the consequent giving of more tetanus antitoxin with possible fatal results. This man had never had any symptoms of allergy to horse serum prior to this time. He had received toxin-antitoxin and two injections of prophylactic tetanus antitoxin several years before in conjunction with treatment of industrial wounds. Undoubtedly these produced his hypersensitivity.

Case 2.—J. F. was admitted to St. Elizabeth Hospital December 8, 1938, having practically blown off his right hand with a shot gun. The wound was so extensive that it required amputation in the middle of the forearm the following day. On admission 1500 units of tetanus antitoxin was given. This man gave no history of sensitivity to horse dandruff or serum. Except for three injections for typhoid in the war he had never received inoculations. Four days after the operation on awakening in the morning he complained of urticaria, difficulty in swallowing, and inability to open his mouth completely. His teeth could be separated only for a distance of 1 cm. Adrenalin was given and the condition improved after a few hours. The next day there was no sign of temporomandibular limitation of movement.

Case 3.—Recently one of us (PLT) was called in consultation by Dr. F. M. Miller, Jr., to see a pneumonia case which exhibited general articular pain most

marked in the temporomandibular joint. This patient had received anti-pneumococcus serum six days previously.

Comment.—These cases illustrate the importance of careful observation and correct diagnosis. If the opinion of the first consultant had been accepted and the patient, on the theory that the stiffness of the jaw was the onset of tetanus, had been given the large dose of tetanus antitoxin recommended, there is little doubt that he would have died of anaphylactic shock. The proper diagnosis and treatment with adrenalin resulted in his leaving the hospital well four days later.

In making a differential diagnosis between the onset of tetanus and a temporomandibular serum arthropathy, certain things must be taken into consideration. The time of onset is of importance. The incubation period of tetanus is in inverse ratio to the severity of the attack. While it is quite possible for a severe tetanus to begin on, or even before the eighth day, cases in which a prophylactic dose of serum has been given are rarely so acute and usually have a longer latent period. Therefore, if the stiff jaw occurs concomitantly with the other symptoms of serum sickness on the eighth to tenth day, the chances are in favor of the symptoms being due to serum and not to tetanus. The character of the stiffness also is quite different in the two conditions. The lockjaw of tetanus is spasmodic. Any effort to separate the teeth results in a snapping together of the jaws, and tapping on the masseter muscle causes a similar reaction. Even a loud noise or a sudden movement may produce the same effect. In the serum arthropathy, on the other hand, the condition is not a spasm but an arthritic limitation of motion. While the teeth can be separated but little and, owing to the pain in the joint, the patient may resist further efforts towards opening his mouth, the spasmodic closing is conspicuous by its absence. There is no reaction to tapping on the masseter muscle. There may, or may not be, local swelling and tenderness over the temporomandibular joint. In serum arthropathies it often happens that the only symptom is stiffness and pain without swelling or tenderness.

The pathologic character of "allergic arthritis" is probably an urticarial swelling of the synovial membrane. In the cases under consideration, this was sufficient to immobilize the temporomandibular joint.

A review of the literature reveals barely a mention of temporomandibular serum arthropathy. The only reference we have been able to find is in Tuft's new textbook on "Clinical Allergy" in his article on serum allergy in which he says: "The temporomaxillary joints are involved more often in serum disease than in rheumatic fever." Nowhere can we find a hint that the condition must be distinguished from the onset of tetanus.

As on the differentiation of these two conditions depends the treatment of the case and often the life of the patient, it seems appropriate to call attention to the similarities and differences between the trismus of tetanus and the rigidity of temporomandibular serum arthropathy.

DISCUSIÓN

Estos casos demuestran la importancia de una observación cuidadosa y de un diagnóstico exacto. Si la opinión del médico consulante ha sido aceptada y aquella del paciente, que el rigor de la mandíbula fué el principio de tétano. Y por eso, se recomendó que se le hubiera administrado una dósis mayor de tétano antitoxina. No cabe la menor duda que el paciente se hubiera muerto de un shock anafiláctico. El propio diagnóstico y tratamiento con adrenalina resultó, que cuatro días después salió del hospital en buena salud. Ciertas cosas deben considerarse cuando el diagnóstico diferencial se hizo entre el principio de tétano y un suero temporomandibular de artropatía. El principio del "shock" es de importancia. El periodo de incubación de tétano es en razón inversa a la ligerez del ataque. Es muy posible que tétano venga con severidad, o aún antes de ocho días, casos en que, una dósis preventativa de suero se haya dado; raramente son agudos y usualmente no tienen un periodo latente. Por lo consiguiente, el rigor mandibular ocurre simultaneamente con otros síntomas de enfermedad del octavo al décimo día. Todo es a favor de los síntomas debido al suero y no al tétano. El caracter del rigor es también diferente en las dos condiciones. La mandíbula rígida de tétano es espasmódica. Cualquier esfuerzo para separar los dientes resulta un cerramiento de las mandíbulas y el tocar el músculo masetero causa una reacción similar, aun ruido fuerte o un movimiento repentino puede producir el mismo efecto. En el suero de artropatía, la condición no es un espasmo sino una limitación artrítica de movimiento. Mientras los dientes pueden ser separados un poco y debido al dolor en la coyuntura, el paciente puede resistir los esfuerzos ulteriores al abrir la boca, el cerrar espasmódico es conspícuo por su ausencia.

No hay reacción al tocar el músculo masetero. Puede y no puede ser hinchazón local y de lo tierno de la coyuntura temporomandibular. En suero de artropatías a menudo sucede que el único síntoma es rigor y dolor sin hinchazón o suavidad.

El caracter patológico de "Allergic Arthritis" es probablemente un hinchazón urticarial de la membrana sinovial. En casos, bajo consideración, esto fué suficiente para inmobilizar la coyuntura temporomandibular. Una Revista de literatura hace mención meramente del suero temporomandibular de atropatía. La única refenencia que hemos podido hallar en el texto nuevo del Dr. Tuft es "Clinical Allergy," en su artículo sobre el suero de alergia en el cual dice: "La temporomaxilaria" las coyunturas se envuelven más a menudo en la enfermedad del suero que la fiebre rehumática. No hay ninguna indicación que la condición debe distinguirse al principio del tétano.

Desde que la diferenciación de estas dos condiciones depende del tratamiento del caso y, a menudo la vida del paciente; luego parece propio llamar la atención a las similiradades y diferencias entre los trismos del tétano y la rigidez del suero temporomandibular de artropatía.

A BRIEF CRITICAL REVIEW OF FUNDAMENTAL KNOWLEDGE CONCERNING THE ALLERGIC DISEASES

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THE modern concept of allergic disease, namely, a pathologic state caused by the interaction of antigen and antibody, originated in the classic monograph of von Pirquet and Schick on serum disease.[40*] It is due these authors, also, to recall that they published their assumption of the above-mentioned principle before that principle had been demonstrated in the experimental state of anaphylaxis in lower animals; that is, previous to the reports in 1907 and 1908 by Otto,[28] Friedemann,[16] Nicolle[26] and Richet[31] on *passive* anaphylactic sensitization.

While von Pirquet and Schick thought their way to their antibody-antigen theory through the analogy of precipitin-production in the lower animal, they seem not to have been satisfied by their findings in the subjects of serum disease as incriminating precipitin in the etiology of that phenomenon. They write (p. 108):

"As we shall see further, serum sickness and precipitin-formation cannot be brought so simply into a casual relationship, because on the one hand precipitin usually appears much later than the illness, while on the other hand even severe symptoms of serum sickness can occur without the formation of precipitin."

However, this apparent contradiction did not shake their faith in their fundamental thesis; they preferred to suggest the possibility that the assumed antibodies responsible for serum sickness were *different* from precipitin. Thus, on page 115 of their monograph, one finds the following:

"The essence of our concept lies in the fact that the 'immediate reaction' and sensitivity on reinjection is an antibody reaction taking place in living tissue (vitale).

"The antibodies that are responsible for it are, however, not identical with precipitin and it is not the formation of the precipitate in the individual that produces the symptoms but a chemical action of another sort between the horse serum and the antibody of the living-tissue (vitale) reaction."

This foresighted conclusion of von Pirquet and Schick received support from the observations of Tuft and Ramsdell[38] upon the occurrence of serum sickness following the injection of normal horse serum in "normal" persons. Such persons were found to produce little or no precipitin nor the other antibodies that appear in the blood of infected

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Address presented before the Fifth Annual Forum on Allergy, Cleveland, Ohio, January 10, 1943. Upon presentation of this address Dr. Coca was awarded the Forum Gold Medal for outstanding contributions to clinical allergy.

*The immunological significance of the incubation period and of the accelerated reaction upon a reinjection of foreign serum had been pointed out by those authors as early as 1903 (Wien. klin. Wchnschr., p. 1244, 1903), although their theory was not so clearly stated in that paper as it was in the monograph.

persons after injection of therapeutic horse serum. The explanation of this different reaction to normal and therapeutic horse serum is lacking.

However, the correctness of the assumption of von Pirquet and Schick as applied to serum disease has now been directly proved through the method of passive sensitization.[19,41]

The "passive serum sickness," as it is termed by Karelitz and Stempien,[19] was first described by Voss[41] as occurring soon after the intravenous injection of the serum of subjects with serum-sickness into perons who had recently (one to nine days previously) received injections of therapeutic horse serum. Since these two injections, antigen and "antiserum," were given in the reverse of the usual order of passive sensitization, Voss referred to the resulting reaction as "inverse serum sickness." The reaction sometimes began before the intravenous injection of the human serum was completed, but usually five to forty-five minutes afterward. Voss observed the reaction in thirty-six children. Karelitz and Stempien reported reactions in fifty-five of the sixty-two patients in whom Voss's technique was applied.

Dr. Karelitz has permitted me to cite the following unpublished observations that bear upon this question. Some of the sera of his patients convalescent from serum sickness contained little or no demonstrable precipitin but a relatively strong property of inducing passive serum sickness; other convalescent sera possessed no property of inducing passive serum sickness but a strong antihorse precipitating power and also the property of passively sensitizing guinea pigs. These observations are not compatible with the identification of precipitin as the specific cause of serum sickness; they provide proof of the correctness of the suggestion of von Pirquet and Schick that has just been mentioned: namely, that there is a specific antihorse antibody which is responsible for the occurrence of serum sickness but which is not identical with precipitin.

In 1906 Wolff-Eisner[42] suggested that hay fever may be an example in certain human beings of a specific sensitivity to otherwise inocuous protein. He wrote:

> "I believe that a uniform concept of hay fever which solves all the posed questions in a satisfying way can be formulated on the basis of the experiences that have been had recently in the field of protein-immunity.
>
> "It has been seen that repeated injections of foreign proteins (of serum, organs, bacteria) lead not to an immunity but to an ever-increasing sensitivity of such a form that upon the first injection slight symptoms or no symptoms appear, that the reaction after the second injection is increased and accelerated, and that after further injections the degree of the reaction further increases."

The suggestion of the allergic nature of bronchial asthma, especially that caused by pollens, was made in 1910 by Meltzer.[25]

No doubt the general acceptance of the allergic nature of hay fever and of bronchial asthma was greatly expedited by the discovery of the specific cutaneous sensitivity, in many of the subjects, to the excitants of those conditions.

While the first demonstration of such sensitivity is credited to Blackley,[2] and this was confirmed by Smith,[35] Schmidt,[34] Noon[27] and others, the systematic diagnostic use of the phenomenon was established by Schloss,[33] who used the scarification or "scratch" technique, and by Cooke,[10] who used the intracutaneous injection method.

The consistent results of these diagnostic tests in hundreds of subjects of hay fever and asthma, confirmed in principle by the clinical relief obtained by avoidance and very often also after a series of so-called desensitizing injections, firmly established the assumption of the allergic nature of those diseases.

The specificity of the allergic cutaneous reactions suggested the existence of antibodies as the essential mechanism of the allergic state and the search for these was begun early.[3,12,14,24,36] Under the influence of the universally accepted assumption of the anaphylactic nature of human allergic disease, the first experimenters in the search for human allergic antibodies employed the technique that had been found most favorable for the demonstration of anaphylactic antibody (precipitin). This technique consists of the injection of the serum of the sensitive individual into a young guinea pig and the testing of the animal after six hours for passive sensitivity to the specifically related antigen. This test could be carried out upon the living animal or upon the excised uterine strip (Dale), which is a somewhat more delicate test-material.

The results of these studies were sometimes positive, and it seems indicative of the unreliability of the method, as it was carried out by some of those early workers, that the positive results were frequently reported with nonantigenic excitants for which no antibodies have since been found by any method.

After the advent of the Prausnitz-Kuestner[30] technique (see below), the qualitative difference between the anaphylactic antibody and the atopic reagin could be demonstrated and the positive results just mentioned could be judged to have been fallacious.

The publication of the well-known paper by Prausnitz and his assistant, Kuestner, was one of the most important events in the history of our subject. That paper illustrates again the value of a bare description of experimental data without theoretic deductions. Prausnitz did not even postulate the existence of antibodies in the serum of fish-sensitive Kuestner, although the passively transferred cutaneous sensitivity was specific; the reason for this caution was undoubtedly his failure to demonstrate the presence of antibodies by the four available means of detecting precipitin—(1) by specific precipitation, (2) by complement fixation, (3) by passive anaphylactic sensitization of the guinea pig, and (4) by specific neutralization of the antigen.

This negative state of mind on the part of Prausnitz was acknowledged privately by him on the occasion of my Berlin address,[4] when I referred to the atopic reagins as having been discovered by Prausnitz and Kuest-

ner. He said to me, "You give me too much credit." One may honor Prausnitz for his desire to apportion credit with quantitative exactness; however, one can hardly exaggerate the importance of Prausnitz's paper, nor should one overlook his scientific courage in making the report of the transfer notwithstanding the failure of the transfer with his own (hay fever) serum and the failure to demonstrate humoral antibodies by the four available methods.

Prausnitz correctly interpreted the negative results with his hay fever serum on a quantitative basis. That failure could have been due to a low content of reagins in the hay fever serum together with the technical fault in his method—testing intracutaneously with 0.1 c.c. instead of 0.01 c.c., which probably spoiled the control tests; or he may have been unlucky in his choice of a recipient in the tests with the hay fever serum.

With a more favorable technique the Prausnitz-Kuestner experiment was next applied in a series of studies[7,20,21] in which allergic antibodies ("atopic reagins") were recognized as qualitatively different from precipitin. The numerous differences between the two antibodies are discussed in detail elsewhere.[8]

The discovery of the atopic reagins provided a tool that could be applied in the classification of allergic disease, which had already been attempted by the author.

CLASSIFICATION OF THE SPECIFIC SENSITIVITIES

Doerr[15] was the first to consider this question systematically, but since he has abandoned his classification it will not be presented here (see Coca[5] for critical discussion). Doerr's suggestion inspired my own original classification,[5] which was as follows:

Hypersensitiveness
(better, Specific sensitivity)

Anaphylaxis — Allergy
(better, Allergic diseases)

Most, if not all, of the critics of this classification have expressed their objections in a way to make it seem that I have denied the fundamentally identical nature of all these phenomena. But that identity is just as well expressed by the covering term "hypersensitiveness" as it would be by the term "anaphylaxis," used inclusively. Thus, this aspect of the controversy over the classification resolves itself into a mere question of definition, which none of the critics has ever fairly stated.

In writing my Tice article[5] I was strongly influenced by the rejection by von Pirquet and Schick of precipitin as the "allergic antibody" in serum disease, and it was with the freedom of thought gathered from their analysis that I studied the evidence concerning the other allergic conditions and reached similar conclusions regarding them.

At that time, while I realized the necessity of assuming the existence of "antibody-like" substances responsible for the allergic state, it seemed to me quite unjustified to speak of those hypothetical substances as antibodies, if for no other reason than the fact that they must be different from the known antibodies. There was, however, another restraining fact; namely, the nonantigenicity of many of the specific excitants of allergic disease. I therefore employed the noncommittal term "mechanism." Thus, I wrote the following:

> "The only conclusion that can be drawn from these facts is that a drug does not produce its peculiar effect upon the hypersensitive person through the usual medium of its toxic action, but through a different mechanism, which is the same in all of the drug allergies."

I suggested that the mechanism of serum disease was the same as that of the drug allergy that appears as an eruption, with other symptoms, after an incubation period following injection of a drug. The studies of Voss and of Karelitz have pointed the way to the investigation of this question.

I have to acknowledge some confusion of thinking in my discussion of the theory of von Pirquet and Schick in the Tice article. When I objected to their theory as an antibody-antigen theory, I was overlooking the fact, of which I was well aware, that they had rejected the known antibody (precipitin) and had postulated some other undefined antibody as the specific cause of the serum reaction. My assumption of another specific mechanism was actually not different from theirs.

The main original basis of my separation of anaphylaxis and allergic diseases was the general failure to identify precipitin (anaphylactic antibody) as the specific mechanism of any human allergic disease. But this negative criterion of differentiation was displaced in the case of the atopic category by the discovery of the specific mechanism of that disease—the atopic reagins.

Another strong, negative mark of differentiation of anaphylaxis and atopy is the general failure to identify unstriped muscle as a human allergic shock-tissue.

With the exception of the mechanism of the atopic group and possibly that of serum disease, the specific mechanisms of the allergic diseases still remain hypothetical.

I have in mind here contact dermatitis and the hypersensitiveness of infection (tuberculin type). As to the former of these, we possess the following information:

1. The excitants are nonantigenic oils and chemicals.
2. The sensitivity of contact dermatitis is limited to epidermal cells.
3. The sensitivity of contact dermatitis is established in epidermal cells only through local contact with the excitant.[37]
4. The sensitivity of contact dermatitis is not mediated by blood-borne antibodies.

These last two conclusions were drawn from experiments carried out by Strauss[37] on monkeys. When two areas of skin were completely separated from each other by surgical operation and only one area was given contact with poison ivy extract, the other area always failed to become sensitized (four experiments, in one of which neither area became sensitive).

One of the mysteries in the field of allergic disease has been the nature of the relief of hay fever subjects that so often is acquired through a series of injections of the respective pollen-extract.

Such injections were first employed by Noon on an empirical basis and the treatment was developed by a number of later observers, also on empirical grounds.

It was clinically well known that the protection resulting from the injections is specific and this fact required the assumption of a specific nature of the protective mechanism. In other words, *the protective mechanism must neutralize either the sensitizing antibody or the antigen.*

The idea that the clinical protection was an effect of desensitization (neutralization of the sensitizing antibodies) was hardly compatible with the known facts regarding the method of treatment. These facts were:

1. The sum total of pollen antigen required for the successful treatment of some hay fever subjects, especially the most sensitive ones, is much too little to neutralize even one-tenth of the circulating reagins.

2. The usual schedule of the injections is not that which is appropriate to the procedure of desensitization but rather to that of immunization.

The finding that the atopic reagins of hay fever are never diminished and may sometimes be increased[20] in primarily treated subjects finally disposed of the possibility that the relief of hay fever after injection of pollen extract is due to a desensitization. And this conclusion *left only one other conceivable explanation of the phenomenon we are discussing; namely, that it is the result of the formation of neutralizing immune antibodies.*

The first step toward the final solution of the problem was made by Cooke and his associates.[11,13] These observers described two kinds of evidence indicating the existence of "a peculiar blocking or inhibiting type of immune antibody that prevented the action of allergen on the sensitizing antibody."

They reported passive protection of sixteen otherwise untreated subjects with hay fever among a series of twenty, through transfusion of blood (quantity not stated) from successfully treated subjects. They also reported that whereas the atopic reagins in the serum of the untreated patient are neutralizable by pollen extract, the same relative quantities of extract fail to neutralize the reagins in the serum of the same patient obtained after successful treatment.

A certain confusion of ideas appears in their report. They proved

the specificity of the "peculiar inhibiting antibody," yet they considered the possibility that this substance could act by exerting an inhibition upon histamine, which, as far as the protection against hay fever is concerned, must be nonspecific.

The next clarifying experiments were contributed by Cohen and Nelson.[9] These investigators, believing that the inhibiting substance of Cooke and his associates is simply an immune antibody specific for the respective pollen antigen, had injections of an extract of ragweed pollen given to two sheep and demonstrated the development of specific neutralizing antibodies in the serum of these animals.

The question was finally and convincingly solved through studies of the sera of treated hay fever subjects by Loveless.[23]

Cooke and his associates and also Harley[18] had concluded that the reaction inhibiting substance was incapable of binding the pollen antigen, but Loveless believed that this conclusion rested on the use, by these observers, of a confusing mixture of the sensitizing (allergic) and the neutralizing (immune) antibodies. It had already been reported[21] that the atopic reagins are incapable of inactivating the respective antigen; hence that portion of pollen antigen in mixtures with hay fever serum which was in loose combination with the reagin was still capable of causing specific reaction in the sensitized cutaneous site.

In order to eliminate this source of error in the neutralization-experiment, Loveless employed the demonstrated fact that the sensitizing reagins are destroyed by heat. Thus, the serum of treated hay fever subjects, after being heated several hours at 56° C, would no longer passively sensitize the normal skin but was found to possess the power of neutralizing the respective pollen antigen.

Loveless could demonstrate the separate existence and different general character of the sensitizing reagin and the immune antibody through another ingenious experiment. It had been shown that the atopic reagins possess a high affinity for receptive tissues,[1,7,22] whereas the usual immune antibodies of lower animals and of man are readily diffusible.[17]

Loveless reports that when a mixture of the serum of an immunized nonatopic person with the serum of an untreated subject of ragweed hay fever was injected intracutaneously into a normal skin, that site was at first insensitive to as much as twenty-five units of ragweed pollen antigen, whereas the control site injected only with the serum of the hay fever subject reacted to as little as one unit. This difference was due to the neutralizing action of the human immune serum in the experimental mixture. However, after twenty hours the site injected with the mixed sera had become fully sensitive to one unit of the antigen, indicating that the immune antibodies had diffused away.

Loveless states* that she has never failed to demonstrate the presence

*Personal communication.

of neutralizing immune antibodies in the serum of successfully treated hay fever subjects, even when the high "constitutional sensitivity" of the patient had prevented the injection of more than relatively small doses of the antigen.

The failure of the specific treatment that is experienced with some hay fever subjects may be due to one or both of two circumstances: the production of neutralizing antibody may be too little, or the shock-organ of the hay fever may be extraordinarily sensitive in those cases.

Those of you who heard the admirable paper by Dr. Loveless yesterday know how beautifully she has completed this picture by showing a general parallelism between clinical improvement or deterioration and the concentration of the blood-borne immune antibodies.

The effort to classify allergic disease has been handicapped by insufficient knowledge of some forms and by some unexplained facts concerning at least one form, bronchial asthma. Many physicians have encountered instances of urticaria, angioneurotic edema, recurrent headache, indigestion, dizziness, and other symptoms that have been demonstrably due to the ingestion of particular foods or to the inhalation of certain dusts or gas; yet the cutaneous tests with suitable preparations of the respective material have resulted negatively. In the first study of the atopic reagins,[7] these allergic antibodies could not be found in the serum of a subject with severe angioneurotic edema known to be due to green pea. What was the nature of the specific allergic mechanism in *that* case?

Bronchial asthma, which is certainly an atopic sensitivity (that is, subject to the atopic hereditary influence), has to be subdivided into the reaginic group and the nonreaginic, or infectious or intrinsic group. What is the allergic mechanism of this *second* group?

The answer to these questions has developed out of an observation that I made, by chance, in 1935, in a case of angina pectoris. The angina in this case had been precipitated by the administration of a moderate dose of dilaudid, which caused such a rapid heartbeat that the pulse could not be counted. Soon afterwards it was noticed that the eating of certain foods caused both angina and acceleration of the pulse, the latter effect always preceding the angina. With the use of this remarkably accurate criterion, a large number of allergenic foods were detected in this case and the angina has been successfully controlled. There was no respiratory symptom in this person and the Prausnitz-Kuestner experiment with all the incriminated pulse-accelerating foods so tested resulted negatively. After a period of avoidance of the allergenic foods in this case, an existing mucous colitis of years' standing disappeared and, with it, a number of other symptoms, some of which had not been thought of as allergic.

The criterion of pulse acceleration was then applied successfully[6] in the diagnosis and treatment (by avoidance) of a number of patients with

migraine and lesser headaches. In nearly all of these there were other symptoms that disappeared with the headaches, and it could be seen that nearly all of the symptoms that had been reported by earlier observers as allergic in *certain* cases were actually allergic in practically *all* instances.

The significance of these findings was amply supported and strengthened by the numerous retests of all of the incriminated foods. With the exception of these retests, the patients remained *completely free* of all of the respective symptoms indefinitely.

Three difficulties, which cannot be discussed here, complicate the practical application of the method. These are the recurrent reactions, the latent period of lost sensitivity resulting from prolonged avoidance of some of the allergenic foods, and the emergence of minor allergens after avoidance of the major allergens.

Cutaneous sensitivity to the culprit foods is entirely lacking, as are the respective atopic reagins, with the exception of those patients who are also subject to atopic sensitivity, and even these do not show cutaneous sensitivity to all of the foods that cause a specific acceleration of the pulse.

This nonreaginic food allergy is not subject to the atopic familial influence and must be separated from the latter for other reasons. It affects a large proportion of the population (Rowe,[32] Vaughan[39] [especially] and Pipes[29]). I found at least 75 per cent affected and suspected a higher incidence. Locke[2a,2b] and his associates report 75 per cent, with a possible additional 10 to 14 per cent.

The specific mechanism of nonreaginic food allergy is plainly different from the atopic reagin; yet it often affects the atopic shock organ of bronchial asthma. And this is at least the *usual* explanation of the so-called infectious or intrinsic asthma. Hence, there seems to be no nonspecific or infectious bronchial asthma. In short, if an asthmatic patient cannot be relieved through the current methods based on the results of cutaneous tests, relief can usually be obtained through the use of the criterion of pulse acceleration, backed by appropriate surgery. This use of surgical procedure will be discussed in a later communication.

UN RESUMEN BREVE Y CRITICO DEL CONOCIMIENTO FUNDAMENTAL ACERCA DE LAS ENFERMEDADES DE LA ALERGIA (POR EL EMINENTE DOCTOR ARTHUR F. COCA)

Nótese que cuando el Doctor Coca concurrió a esta asamblea se le presentó la medalla "Forum Gold Medal" por sus sobresalientes contribuciones a la clínica de alergia.

El Doctor Coca, brevemente, discutió la historia del desarrollo sobre el concepto moderno de la alergia como un estado patológico causado por la entrerección del antígeno y anticuerpo como también sobre la aplicación de este concepto a las varias condiciones clínicas, también se demostraron,

el desarrollo del dérmis, el transferimiento pasivo de las pruebas y, la clasificación de las sensitividades especificas. El Doctor Coca habló sobre el fundamento de diferenciación de la anafilaxis y atopía. El mecanismo específico del contacto de la hipersensitividad del dérmis y bacteria que permanecen particularmente hipotéticos. El desarrollo de nuestro conocimiento de la naturaleza de la desensitización por la concentración de la sangre que lleva los anticuerpos inmunos, ésto ya se ha presentado claramente, El Doctor relata las observaciones que le hicieron concebir la idea de una nueva categoría de las enfermedades de la alergia—"Familial Nonreagenic Food-Allergy" cuyo mecanismo es verdaderamente distinto de la reagina atópica.—F.W.W.

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OUTBREAK OF GLUE DERMATITIS

An outbreak of glue itch among workers in the plywood and laminating industries is causing much lost time in war plants making planes, gliders, propellers and other airplane accessories, Dr. Louis Schwartz, Dr. Samuel Peck and Dr. John E. Dunn, of the U. S. Public Health Service report.

Irritating substances in the glues cause the trouble. Urea-formaldehyde and phenol-formaldehyde resin adhesives caused most of the trouble in the plants inspected, but glues with such harmless-sounding names as gelatin glue or casein glue may have irritating chemicals added.

For treatment only soothing wet dressings, such as boric acid solution or Burrow's solution, should be used during the acute stages when there is swelling, blistering and oozing of the skin. In the later stages when the eruption begins to dry and crust, mild fatty-base ointments should be used.—*Science News Letter*, July 17, 1943.

DERMATITIS VENENATA

Report on Allergy Clinics in the Fourth Service Command

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DISABILITY for poison ivy dermatitis is important in civilian municipalities.[2] Of even greater consideration is the disability which removes a soldier from daily duty. The training programs of today's army have been paced by the need for well trained and conditioned troops. Any interruption of that training program can seriously interfere with our military progress. The disabled soldier is absent from duty as surely as the soldier absent without leave.

One of the most common causes of disability, either partial or complete, has been dermatitis venenata due to poison ivy. The signs and symptoms of such lesions are sufficiently well known to warrant only brief mention in these paragraphs. It can be correctly assumed that 60 per cent of the population possess a sensitivity for this plant. The remaining 40 per cent are not affected by its contact, as they possess a natural immunity which enables them to remain free of symptoms subsequent to exposure. The sensitive patient complains of marked burning, itching and smarting at the site of contact. The onset of these initial symptoms is usually noted a few minutes or a few hours after exposure. Vesiculation, weeping and redness follow shortly. The hands, face, neck and arms are the sites most commonly affected, but any part of the skin may be later involved. Contamination of clothing and other wearing apparel may be productive of symptoms appearing during a season when the plant itself is not abundant.[3]

The severity of the lesions is dependent upon the degree of sensitivity possessed by the patient, as well as the amount and duration of exposure. In the usual training camp, little control can be exercised over the amount of exposure to poison ivy that a soldier will experience. Maneuver problems and routine exercises bring the soldier into very close and abundant contact with the weed. Since many of these training programs in the field are held as night problems, the ability to recognize the growth as poison ivy is not a particular valuable asset for prevention. Local application of various lotions and ointments prior to expected exposure has failed to afford adequate protection. Attempted desensitization in an effort of prophylaxis has likewise been unsuccessful as a general rule; however, this latter step holds more promise than the protective lotions or creams.

Eradication of the weeds locally at some stations has been attempted in an effort to decrease the amount of available contact. This measure has undoubtedly been of some value, though not to the degree commensurate with the amount of labor and detail connected with this procedure.

We wish to present the efficiency with which 2,544 patients with poison ivy dermatitis were treated during the summer of 1942. This report is based on a questionnaire submitted to 32 stations in the Fourth Service Command. When the Allergy Section of the Surgeon's Office, Fourth Service Command, was established in March, 1942, it was known that much disability had resulted in previous years from poison ivy sensitivity. The necessity of providing adequate prevention or treatment for the many cases that were expected prompted the institution of a plan for active treatment of this sensitivity. Past experience with a five per cent alcoholic extract of poison ivy leaves had produced exceptionally good results in military personnel.[1] Preparation of this extract was completed at the Fourth Service Command Laboratory according to the method of Cooke and Spain.[4] Each of the 32 stations was furnished an adequate supply of this concentrated extract for use during the summer of 1942.

Dermatitis venenata was most troublesome during the months of June and July. One station revealed a very interesting percentage by maintaining accurate and complete poison ivy records. At that training center, dermatitis venenata was the established diagnosis in 15 per cent of all dispensary patients seen during this two-month period. The institution of therapy at each dispensary was based upon the directions for administration which accompanied each vial of extract. Dilution of this concentrated extract just prior to each injection furnished a 1-10 solution. Daily administration of gradually increasing amounts was the usual routine. Since no determination of the degree of sensitivity can be made for each patient, variations from the suggested schedule were dependent upon each preceding injection. Great care was exercised to insure the safety of this therapy and to prevent the aggravation of the skin lesions by too enthusiastic measures. In most instances, a dosage of 0.4-0.5 ml of the 1-10 dilution was reached by the fourth day of therapy. Rarely was it necessary to continue the administration of the poison ivy extract longer than four or five days.

Table I summarizes the important findings of this report. Of the 2,544 patients diagnosed as poison ivy dermatitis, 2,422 (95 per cent) were military personnel. The remaining 122 (5 per cent) were civilian dependents of the army. The number of patients treated at each station was dependent upon several factors. Of chief consideration, of course, is the concentration of troops at some posts. Other contributing points were the type of training at each station and the geographical location in some instances.

Past experience with poison ivy therapy has shown that the benefit of alcoholic extract is enhanced by early administration. The majority of the patients gave a history of having had previous complaints of dermatitis upon exposure to poison ivy. For these reasons, patch testing was not a pre-requisite to the administration of therapy. This may not be in accord with strict clinical procedures, but our problem was one, not of clinical

research, but one in which the preservation of time was all-important. In those instances where there was any doubt as to the diagnosis or source of the dermatitis, patch testing was done. We do not wish to convey the impression that indiscriminate administration of poison ivy extract was advised in all dermatologic complaints.

We were interested in determining how many soldiers with poison ivy dermatitis could be maintained on an effective duty status. Of course, the severity, extent and location of the skin lesions were prime factors influencing the disposition of these patients. Of the total number of patients diagnosed, 1,748 were adequately given treatment at their dispensary. These patients all remained on full duty during the course of their dermatitis. Though we were unable to obtain accurate information concerning the location and extent of all lesions, an expression of the severity in each patient was recorded. The dispensary cases show a predominance, as would be expected, of the mild and moderate lesions. Seven hundred and seventy-seven of the 1,748 dispensary-treated cases were classified as mild. Seven hundred and fifty-three patients treated while remaining on duty were of moderate severity. Dermatitis venenata in a markedly severe degree was diagnosed in 218 patients. The comparatively low number in this classification is perhaps an indication that many severe dermatitis cases were referred to the hospital for therapy and care. The hospital admissions, however, do not entirely agree with this suggestion. It must be admitted that no definite limitations nor points for classification were outlined. The opinions of the attending medical officers have been accepted for this report.

A total of 754 patients with dermatitis venenata was admitted to the hospital wards. These patients were unable to remain on a full-duty status, because of the extent and location of the lesions or because of the severity of their complaints. Some few diagnoses may have been made on patients admitted to the hospital for other causes, but our records do not reveal this detail. A classification of mild dermatitis was recorded for 65 patients on the hospital wards. This comparatively low figure is in agreement with the expression that the greatest majority of mild lesions respond in a satisfactory manner to dispensary treatment. Four hundred and seventeen patients were admitted to the hospital with lesions of moderate extension. This group composed the largest number of patients under hospital therapy. The personal discrepancy in estimating the severity of lesions undoubtedly accounts for the size of this classification. The remaining 272 hospital patients were grouped as severe.

The average period of hospitalization has varied from 16.1 days at one station to 3.6 at another. This is quite surprising, since these two posts are about equal in size and are geographically similar. The average hospital stay for each patient in all stations has been recorded as 8.7 days. Table I reveals that seven stations did not find it necessary to remove any patients from duty because of dermatitis venenata. The average length

TABLE I. SUMMARY OF FINDINGS

Post or Camp	Total Patients		Dispensary			Hospital			Average Hospital Days	Treatment with Extract	Average Number Injections per Patient	Results				
	Army	Civ.	Mild	Mod.	Sev.	Mild	Mod.	Sev.				Good	Fair	Poor	None	Inc.
A	2	0	0	2	0	0	0	0	0	2	3	2	0	0	0	0
B	4	9	7	6	0	0	0	0	0	5	2	5	0	0	0	0
C	95	0	42	8	0	3	27	15	10.7	32	2.5	3	7	15	2	5
D	75	3	6	26	5	2	3	20	8.4	62	3.7	49	5	5	2	1
E	128	45	26	116	31	0	0	0	0	173	5	152	21	0	0	0
F	258	0	11	97	26	0	61	63	7.7	174	3.5	15	105	45	0	9
G	6	0	1	1	0	0	2	2	5	2	3	0	2	0	0	0
H	95	9	27	0	0	5	56	16	10	36	4	23	12	0	0	1
I	4	0	0	2	0	0	0	2	4	2	4	2	0	0	0	0
J	2	8	3	6	1	0	0	0	0	10	6	10	0	0	0	0
K	24	4	14	6	2	0	5	1	9.5	26	3.2	9	11	3	2	1
L	93	6	4	20	5	4	41	25	9.8	42	3	10	26	6	0	0
M	115	4	11	98	7	0	3	0	6.6	8	4	0	0	8	0	0
N	7	2	2	4	0	0	2	1	5.6	7	2	7	0	0	0	0
O	26	0	0	0	0	3	7	16	16.1	26	4	0	6	0	2	18

TABLE I. SUMMARY OF FINDINGS—*Continued*

P	93	2	49	26	8	3	6	2	14	19	4.8	10	5	3	0	1
Q	10	0	3	6	0	0	0	1	9	8	5	8	0	0	0	0
R	292	0	186	66	28	2	7	3	7.3	264	4	248	10	3	2	1
S	43	13	8	27	17	0	1	3	5.5	56	3.4	55	0	1	0	0
T	3	0	0	1	1	0	0	1	13	2	5	2	0	0	0	0
U	40	0	7	16	5	1	4	7	10.5	3	5	0	3	0	0	0
V	8	3	4	7	0	0	0	0	0	11	5	11	0	0	0	0
W	15	11	7	3	1	6	4	5	9.2	13	5.2	10	3	0	0	0
X	127	1	40	15	17	2	15	17	7.7	29	4	9	11	7	2	0
Y	299	0	95	43	0	23	101	37	10.5	299	5	226	54	19	0	0
Z	11	0	5	1	0	1	4	0	3.6	11	3	8	1	1	1	0
AA	5	0	3	1	0	0	0	1	8	2	4	1	1	0	0	0
BB	15	2	2	5	6	0	0	4	11.5	17	4	10	2	1	3	1
CC	378	0	169	92	14	10	69	25	9.6	378	5	278	31	56	13	0
DD	58	0	13	31	14	0	0	0	0	58	5.2	30	18	6	4	0
EE	61	0	32	21	0	0	3	5	5.6	44	6	37	7	0	0	0
FF	30	0	0	0	30	0	0	0	0	30	3.2	30	0	0	0	0
Total	2422	122	777	753	218	65	417	272				1260	341	179	33	38
	2544		1748			754			8.7	1851	4	1851				

of hospitalization, therefore, has been computed from 25 stations at which dermatitis venenata was a source of admission.

An interesting and encouraging comparison of therapeutic methods was made at one large station hospital. Fifty patients with lesions of near equal severity and character were designated for this study. Alternate cases were treated by alcoholic extract or by local applications. The purpose of this comparison was to determine the average length of hospitalization resulting from these two methods of treatment. In the group receiving alcoholic extract as the only therapeutic measure, there was an average of 8.4 hospital days per patient. The group in whom local applications of lotions and creams were used recorded an average stay of 11.3 days per patient. Though this average difference of three days per patient may not seem remarkable, it is impressive from such a small group.

Specific therapy was extended to 1,851 (73 per cent) of the 2,544 patients diagnosed as dermatitis venenata. It was the policy at some stations to use local therapeutic applications in the very mild lesions. A few clinics were of the opinion that the use of poison ivy extract was indicated only during the stage of vesiculation. Subsequently, 27 per cent of the total were treated by measures other than alcoholic extract. The mild degree of the lesions or the delayed period at which the patient appeared in the dispensary prompted the omission of specific measures.

At this point, a brief mention of the duration of therapy is indicated. It has been shown that the average period of hospitalization has been 8.7 days. This should not imply, however, that administration of the diluted extract was a daily procedure during all of this period. The general response to specific therapy was rapid in those patients who received beneficial results. From all thirty-two clinics, the highest average of injections per patient at one station has been recorded as six. The lowest average number of injections reported by another clinic was two. In the usual case, relief and subsidence of symptoms were sufficient in four or five days to permit discontinuation of therapy. An average of four injections per patient has been recorded for all patients with dermatitis venenata receiving alcoholic extract. The therapy and results of hospital and dispensary patients have not been considered individually for each group. The only differentiation in tabulating the findings for these patients has been in classifying them as "on duty" (dispensary) or "off duty" (hospital).

The largest obstacle in accurate evaluation of results in any therapeutic test is the difference in personal opinion. Some medical officers were quite enthusiastic about the use of alcoholic extract and this optimism may have influenced their appraisal of relief. Others, however, were hesitant to use this extract, because of their past experiences with commercial extracts. With these two approximately even groups as a source of supply, the recorded results can be accepted with a good measure of

confidence and reliance. In the 1,851 patients receiving extract therapy, classification of end results has been the opinion of the dispensary or ward officer who followed each case to its satisfactory or unsatisfactory conclusion. Good or satisfactory results have been those in which the relief of symptoms and duration of acute dermatitis have been prompt and uncomplicated. There were 1,260 (68 per cent) in this classification. Fair results have been designated in those cases receiving some distinct benefit from extract therapy, though not so rapidly nor so thoroughly to be included in the former classification. Three hundred and forty-one patients (18.4 per cent) were reported as having a result specified as fairly satisfactory. In those 179 patients (9.7 per cent) included in the poor result group, the lesions of dermatitis venenata responded in a very slight degree, but the improvement was slow and prolonged. No result was obtained from the use of alcoholic extract in thirty-three patients (1.8 per cent). This group should perhaps have been included with those patients in the preceding classification. An increase in the severity of lesions was noted by thirty-eight patients (2.1 per cent) subsequent to extract administration. These reactions were characterized by an aggravation of the existing symptoms. At no time was there associated evidence of constitutional reactions other than soreness and swelling at the site of some injections. Of the 1,851 patients treated with alcoholic extract of poison ivy leaves, 86.4 per cent received satisfactory or fairly satisfactory benefit therefrom.

COMMENT

At some of the thirty-two clinics, attempts to use this extract in prophylaxis have met with encouraging results. Camp EE reported their experience with the administration of alcoholic extract to a group of 30 known sensitive soldiers. Small, gradually increasing amounts of diluted extract (1-100 and 1-10) were injected subcutaneously for a few weeks prior to expected exposure. Each of these soldiers had previously been incapacitated because of dermatitis venenata. The initial dosage in each instance was 0.2 ml of the 1-100 dilution. After eight injections at twice weekly intervals, the top dosage of 0.5 ml of the 1-10 dilution was reached. There was no local or general evidence of over dosage at any time. Definite known exposure while on a short maneuver problem produced typical lesions of dermatitis venenata in only one of the thirty subjects. No expression was made concerning the duration of protection thus afforded to the other twenty-nine soldiers. The answer to this important point would determine the advisability of continuing such prophylactic measures on a larger scale.

The rapidity with which local symptoms were relieved by alcoholic extract therapy was stressed by the majority of clinic reports. Marked itching, burning and smarting were alleviated by the first or second injection. This beneficial response was an all-important feature for the comfort of each patient. The ultimate duration of the lesions was also

shortened by this factor. Absence of local irritation under therapy prevented to a great degree subsequent complications that may have arisen without this initial therapeutic response.

Camp M was the only station declaring this method of therapy to be of "little value." Of the 119 cases of poison ivy dermatitis at that clinic, only eight of them were treated with extract. These were reported as obtaining a "poor" result. At Fort O, eighteen of twenty-six patients noted an increase in the severity of their lesions with extract therapy. Administration of the extract in correct dilution and in the advised low dosage would have resulted in a different classification. Specific instances were cited in Fort O's report, wherein the alcoholic extract was administered in the correct unit dosage but in the supplied strength (5 per cent). These reports have been included in this comment to emphasize the care and attention that must be utilized with each individual patient.

Fort C offered the information that there was no recurrence of lesions noted in patients who had received extract therapy. This may, in part, be an indication of the duration of relief and protection upon further exposure. Camp T reported that their one severe dispensary patient had cleared completely in five days with extract therapy. No time was lost from duty. This same patient in 1941 had been hospitalized for twenty days with dermatitis venenata. Treatment during that attack consisted of local applications of lotions and wet packs.

SUMMARY

The use of a 5 per cent alcoholic extract in the treatment of dermatitis venenata is discussed. The therapeutic response has been very encouraging, inasmuch as 68 per cent were classified as good and 18.4 per cent as fair results. Clinical reports from thirty-two stations in the Fourth Service Command were tabulated. In all 2,544 patients were diagnosed as dermatitis venenata due to poison ivy. Of these, 1,851 were treated with this extract. Emphasis is placed upon the parenteral administration of the extract to military personnel on a duty status. Of the 2,544 patients, 1,748 did not miss a day of duty because of dermatitis venenata.

SUMARIO

En resumen, el propósito de este trabajo es el indicar que el uso de un cinco por ciento de extracto alcohólico en el tratamiento de dermatitis venenata se ha discutido a menudo. El tratamiento terapéutico ha sido sumamente favorable, en cuanto el 68 por ciento se clasificó como bueno y 18.4 por ciento como mejor resultado. Relatos de clínica se tabularon de trienta y dos estaciones del "Fourth Service Command." En todos los 2,544 pacientes que se les hizo el diagnóstico como dermatitis venenata debido a la "hiedra" venenosa; de estos, 1,851 se les hizo el tratamiento con esto extracto. Decimos enfáticamente, que la administración parenteral del extracto fué administrada al conjunto de soldados durante horas de em-

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DE-ALLERGIZATION VERSUS HYPOSENSITIZATION

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(Concluded from July-August issue)

DE-ALLERGIZATION BY SPECIFIC SKEPTOPHYLACTIC METHODS ACTING THROUGH MICROSHOCKS

As is well known, the skeptophylactic method, according to Besredka,[3] achieves clinical insensitiveness (so-called anti-anaphylaxis) by means of intravenous, intraspinal, intraperitoneal, subcutaneous, rectal, or oral administration of antigens. It is important to note that the manner in which the antigen is administered (whether parenterally or orally) determines the mode and duration of the protection.

Skeptophylactic De-allergization by the Parenteral Route.—Proof that the parenteral skeptophylactic methods give rise to a de-allergization, although only partial and temporary, rather than to a condition of temporary hyposensitization, is to be found in the following animal experiments:

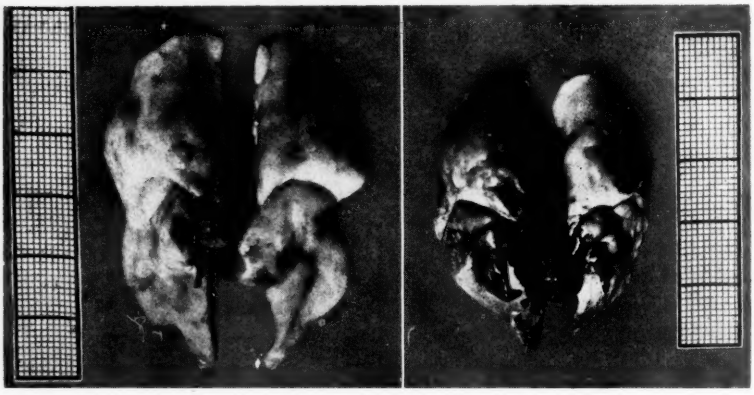
When an animal previously treated by skeptophylactic methods is again allergized, this time passively, by means of specific antiserum, it has been shown by Weil and Coca[33] that the same quantity of antiserum must be used as would have been necessary to render an unprepared guinea pig anaphylactic.

There is further proof of de-allergization rather than of hyposensitization in guinea pigs so prepared and clinically refractory to anaphylactic shock. We[28] found that in the course of the lung perfusion experiment, the lungs of these animals did not react in any way (Figs. 1 and 2). Nevertheless, we may speak only of a partial de-allergization in the case of animals thus prepared, for their uteri still manifested a clear-cut specific antigen sensitiveness, and hypersensitiveness could be passively transferred by the blood serum.

We should like to explain this striking occurrence in the following manner. The principal shock organ of the guinea pig (the bronchioles and the lungs) possesses a greater avidity for the antigen than does the uterus, provided the antigen is administered intravenously in less than shocking doses. It is in the lungs, therefore, that the first antigen-antibody reaction takes place: this is followed by antibody satiation, as demonstrated by the negative outcome of the lung perfusion experiment. Under certain conditions (see below), this partial and temporary de-allergization can be converted into a state of total and permanent de-allergization.

The de-allergization of shock tissues by skeptophylactic measures can be demonstrated not only *in vivo* but also *in vitro*. If we add to a uterine horn of an egg-white sensitized guinea pig a 1:10,000 dilution of egg

white, there will be an immediate reaction under the Schultz-Dale technique. Using the other uterine horn, but adding the egg white in a very dilute form (1:1,000,000) and slowly increasing the concentration to 1:200



LUNG PERFUSION TEST

Fig. 1. Positive result: maximally expanded lung of guinea pig allergized to horse serum, after anaphylactic shock due to introduction of specific antigen.

Fig. 2. Negative result; no response of lung of allergized guinea pig de-allergized by skeptophylactic method.

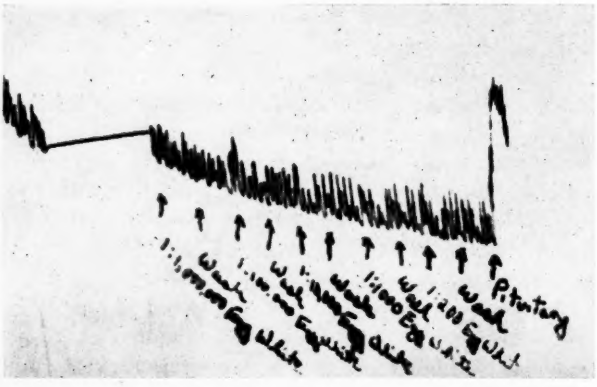


Fig. 3. De-allergization by skeptophylactic method. In Schultz-Dale test, uterine horn of guinea pig allergized to egg white will not react to concentration of 1:200, provided this is reached gradually. Control horn reacted readily to 1:10,000 dilution.

there will be no anaphylactic reaction of the smooth muscle at all, showing that complete antibody satiation has taken place (Fig. 3). In the Schultz-Dale test, the uterine horn of a guinea pig allergized to egg white will not react to concentration 1:200, provided this is reached gradually. The control horn will react readily to 1:10,000 dilution.

When de-allergized in this manner, the uterus will preserve its specific insensitiveness for the duration of its viability.

Skeptophylactic De-allergization by the Oral Route.—In numerous experiments with a great variety of antigens we have shown, as first demonstrated by Besredka, that a period of about two days is necessary to achieve skeptophylactic de-allergization of the guinea pig by means of oral administration of the antigen. Furthermore, we noted the interesting result that animals protected in this manner must be considered completely de-allergized—as evidenced by the absence of reactions not only in their principal shock organ (the lung) but also in the uterus, and by the failure of passive transfer.

We offer the following working hypothesis to explain how skeptophylactic preparation by either route succeeds in rendering tissue antibodies incapable of reacting at least in the principal shock organs. The appropriate administration of small quantities of antigen elicits so-called microshocks (antigen-antibody reactions) that, although clinically not perceptible, do suffice temporarily to bind the tissue antibodies. Newly formed antibodies are then, in turn, satiated by antigen, either repeatedly administered at short intervals by the parenteral route, or slowly absorbed from the gastro-intestinal tract when the oral route is used. However, we should not like to consider this glutting as a merely quantitative chemical process; we are of the opinion rather that the microshock goes so far as to cause an alteration in the reactivity of the antibody-forming organs. In other words, the microshock is followed not only by loss of antibodies owing to satiation, but also by an arrest of antibody production, thus transforming an allergic organism into one having a normal sensitiveness.

It is very interesting to note that skeptophylactic intravenous injections, performed at short intervals, bring about a state of de-allergization that is only partial—i.e., it is limited to the principal shock organ. On the contrary, administration by mouth, with slow satiation by antigens, brings about a state of total de-allergization. In both cases, parenteral or oral de-allergization is at first only temporary. However, the peroral method, when systematically followed for a period of from one to two weeks, leads to a state of permanent de-allergization.

METHODS OF SPECIFIC DE-ALLERGIZATION

The methods of specific de-allergization can be subdivided as follows: spontaneous de-allergization, specific shock therapy, and specific skeptophylactic measures.

Spontaneous De-allergization.—In cases in which the hypersensitiveness has existed for only a short time, mere avoidance of the allergen may suffice to bring on complete de-allergization. This almost always takes place following passive allergization of human beings and animals, as in

the Prausnitz-Kuestner test, for instance. In all such cases, the de-allergization results from the disappearance or destruction of the passively introduced antibodies. A further example is the de-allergization of patients with mild food allergy by means of daily ingestion of small quantities of the given food. This is often seen in children hypersenstive to milk, eggs, and other foods. Equally good results can be obtained in mild contact dermatitis of allergic origin by permitting the patient to continue the work in which he is exposed to the known causative allergen. (While both examples cited are usually referred to as methods of hyposensitization, we are of the opinion that they are based on the principles of de-allergization).

Specific Shock Therapy.—The rationale of specific shock therapy is to overload the organism with a massive dose of the antigen, thereby producing anaphylactic shock. While this procedure usually results in permanent de-allergization, it must be strictly avoided because of the extreme danger involved. In cases of extraordinary hypersensitiveness, however, it sometimes unintentionally occurs that a reasonable dose of the antigen produces a severe constitutional reaction that will frequently be followed by a state of complete insensitiveness often lasting for months.

Specific Skeptophylactic Methods.—Since spontaneous de-allergization cannot be relied upon and specific shock therapy is considered dangerous, the methods referred to here as "specific skeptophylaxis" are recommended as the treatment of choice. They are based on the animal experiments of Besredka.[2] Administration of a small quantity of the antigen will protect the animal against anaphylactic death from a lethal shock dose of antigen, provided that, for the route employed, the proper time relationship and dosage are maintained. According to Besredka's fundamental studies, all routes of administration (intravenous, intraperitoneal, subcutaneous, intraspinal, intracerebral, oral, rectal) are feasible in experimental animals. In human beings, however, only oral and subcutaneous skeptophylaxis are recommended as safe and effective.

In the following pages the more important methods based on skeptophylactic principles are discussed. The majority of students in this field classify them under the heading of hyposensitization. The experimental and theoretic reasons that induce Urbach to include them under de-allergization were given above.

Besredka called this type of protection anti-anaphylaxis to designate the state of insensitiveness achieved in the specific manner described. The term skeptophylaxis (from the Greek σηπτός, "stroke of lightning" and φύλαξίς, "protection"* was applied to this method by Lambert and his associates and has been more or less generally accepted. Skeptophylac-

*In this connection, we must call attention to the erroneous etymologic derivation given in the medical dictionaries: σκεπτικός, "doubtful."

tic treatment results in a prompt temporary protection against anaphylactic shock or other allergic manifestations, and further, if the treatment is continued, in the permanent disappearance of the allergic state as a result of the loss of cellular antibodies.

This concept of the mechanism of skeptophylaxis is not shared by Besredka, the brilliant discoverer of the method. He is of the opinion that the process involved is not one of immunity, but only of detoxification. However, the results of Weil and Coca's[33] experiments and of Urbach's lung perfusion tests in skeptophylactically protected animals, demonstrating the loss of specific cellular antibodies (de-allergization), prove that a true antigen-antibody mechanism is implicated.

(a) *Parenteral Routes.*—Skeptophylactic methods utilizing the subcutaneous route have long been employed in treatment of hypersensitiveness to serum. For example, first a minute quantity (0.1 c.c. of a 1:10 dilution) is injected intracutaneously; fifteen minutes later, 0.5 c.c. of undiluted serum is given subcutaneously (if no untoward reactions occur); then, at intervals of ten minutes, successive subcutaneous injections are administered in steadily increasing doses—1 c.c., 2 c.c., 5 c.c., 10 c.c.—until finally the necessary amount of serum has been injected subcutaneously.

Intravenous skeptophylactic methods, on the other hand, have not, as yet, received any practical acceptance, despite the numerous modifications that have been suggested. This is because of the possible danger of severe or fatal constitutional reactions following injection of even a moderate dose. The method has as its aim the gradual neutralization of the antibodies by administration of the antigen in subthreshold doses of slowly increasing concentrations at intervals of only several hours. Attempts have been made to minimize the danger by employing very high dilutions of the antigen and by giving the injections at a very slow rate. Sicard, Paraf and Forestier inject a small quantity into an arm vein below a tourniquet thus preventing the antigen from entering the circulation too rapidly; after five minutes the tourniquet is gradually loosened, with the result that the injected substance now enters the circulation slowly and in high dilution; ten minutes later the full therapeutic dose may be injected.

During the past few years many attempts have been made to achieve insensitiveness within one or two days by means of subcutaneous or intracutaneous injections, given at very brief intervals. These methods were termed "rush desensitization" by Freeman[11]; however, since they are actually based on skeptophylactic principles, they are discussed here. Freeman,[11] Waldbott and Asher,[31] Bray[5] and others have reported excellent results in hay fever; Freeman[11] in a patient with asthma due to fish, horses and molds; Hart[12] in a case of asthma attributed to cats; Ulrich, Hooker and Smith,[26] Corcoran[7] and Urbach[29] in treatment of hypersen-

sitiveness to insulin. All these authors have stressed the very rapid attainment of insensitiveness.

The same method can also be employed in drug allergies. Thus, Urbach was able to prevent nitritoid crisis from arsphenamine, for example, by a similar technique. First, an intravenous injection of 0.005 gm. of neoarsphenamine is given, after five minutes a dose of 0.015 gm., followed five minutes later by 0.05 gm., and after another two minutes by 0.1 gm. If the patient tolerates these doses well, this procedure is continued on successive days with very cautiously increased doses. However, if any one of the injections occasions any kind of reaction whatsoever, the treatment is stopped for that day, and is resumed after a day or two with a smaller and very slowly increasing dosage. In order to avoid repeated introduction of the needle, we use one that is equipped with a stylet and that can stay in the vein throughout.

For the present, at least, the "rush" methods are to be employed only in well-equipped hospitals and under the supervision of experienced physicians. The danger inherent in them must always be borne in mind. According to our own observations, as well as those of other investigators, the danger is decreased to a certain extent when small amounts of epinephrine (0.05 c.c.) are mixed with the antigen before injection.

In the management of cases of specific allergic dermatitis, asthma, and rhinopathy, Urbach has employed the skeptophylactic principle in a modified technique: two injections were given daily—a very weak dose in the morning, followed six hours later by a considerably stronger one. The following case histories will illustrate the procedure.

Two female workers in the nickel industry, who had been suffering from widespread dermatitis for months, had a definite eczematous reaction to patch tests with even a 1:1,000,000 dilution of nickel sulfate. De-allergization was achieved by the daily administration of two subcutaneous injections of nickel sulfate solutions. The first, at 8 A.M., was 0.1 c.c. of a 1:100,000,000 dilution, while the second at 6 P.M. was of 1:1,000,000 strength. By gradually increasing the concentration, we arrived at a strength (1:100) that induced strong local or focal reactions. Within seventy-two hours these had disappeared. When therapy was resumed even with a cautious increase in the dosage, reactions appeared that necessitated repetition of given strengths. Treatment was stopped when a 1:700 dilution in the morning and a 1:70 dilution in the afternoon was reached. At this time a patch test with an 11 per cent nickel sulfate solution evoked only a very mild local reaction. Almost every normal skin will show some response to this concentration. The patients then returned to work and were able to continue at it with impunity, provided they did not put their hands directly into the nickel bath. A follow-up ten months later revealed that they responded with only a trifling reaction to an 11 per cent nickel sulfate patch test.

(b) *Oral Route.*—The oral skeptophylactic method has proved of great value in the treatment of both drug and food allergies.

Thus, Heran and Saint Girons[13] successfully employed measures amounting to oral de-allergization in patients with hypersensitiveness to

aspirin and quinine; Urbach, in cases of hypersensitiveness to iodine, quinine and other drugs.

The following case history is presented for the purpose of illustrating the technique employed by us.

A woman with asthma had been taking 0.5 gm. of potassium iodide for months, with good symptomatic results. She eventually acquired an exanthem due to hypersensitiveness to iodine. Efforts at oral hyposensitization resulted in new and severe skin manifestations. We therefore instituted a skeptophylactic technique, administering as the first dose on the first day 0.005 gm. of potassium iodide. Every forty-five minutes this dose was increased by 0.01 gm., until sixteen doses had been administered. The peak dose on the first day was 0.15 gm., and the total amount given on that day was 1.205 gm. On the second day we began with 0.01 gm.; the dose was increased each time by 0.015 gm., and a total of 1.89 gm. was thus administered without untoward effect. On the third we began with 0.1 gm. and increased the dose by 0.018 gm., administering a total of 3.76 gm. on that day. From that point on 0.5 gm. of potassium iodide was given three times daily.

It is clear that a similar basic principle is involved in the methods in which infinitesimal quantities of an allergenic food (milk, egg, et cetera) are administered by mouth forty-five minutes before that food is eaten.

But even minute amounts of allergenic foods may elicit the most alarming symptoms. For this reason, Pagniez and Vallery-Radot[20] modified the procedure by giving the patients not the natural food proteins, but ordinary commercial meat peptone, forty-five minutes before eating the allergenic food. These authors reported satisfactory results with this method in cases of urticaria, strophulus, and angioneurotic edema. Auld and Luithlen, however, were unable fully to confirm these findings. Auld, therefore, prepared two kinds of peptones, one of animal and one of vegetable origin, and combined them when necessary. It was Luithlen,[18] however, who first recognized the importance of employing a strictly species-specific digestion product for effective skeptophylactic action. Thus a strictly species-specific allergy to cow's milk cannot be controlled with meat peptone. Luithlen logically prepared a variety of species-specific animal and vegetable protein digests for therapeutic use. Moreover he had preparations made in which the digestion of the protein was carried beyond the stage of proteoses, while still retaining the specificity of the protein from which it was derived. Luithlen, however, was not able to perform the necessary immunologic and clinical studies with his preparations, since he died shortly afterwards.

After some years of experimental work, Urbach[27] presented proof that in cases of specific food protein allergy only the specific protein derivatives called propeptans, administered by mouth, have a skeptophylactic effect and consequently will give rise to permanent de-allergization. Furthermore, he demonstrated that these preparations can be used for diagnostic identification of the allergens.

PROPEPTAN THERAPY

Propeptans are preparations derived from the individual proteins by digestion with hydrochloric acid, pepsin and trypsin. They contain proteoses in a certain amount, but are rich in peptones; simpler nitrogen compounds are present only in small percentage.

Urbach has shown that a guinea pig highly sensitized to egg white can be protected against usually lethal anaphylactic shock by a preliminary injection or feeding of chicken egg propeptan, while other propeptans and even chicken-meat propeptans are totally inefficacious. The strict specificity of the propeptans can also be demonstrated by means of the Schultz-Dale test; the uterus of a guinea pig allergized to hen egg propeptan contracts after addition of only this propeptan and not on addition of a propeptan derived from any tissue of the hen (Urbach and Kitamura[30]).

In view of the fact that the uterus of a guinea pig allergized to egg-white does not react to the addition of egg propeptan in the Schultz-Dale test, W. Jadassohn and Schaaf[15] have concluded that the propeptans are not species-specific. Urbach and Wolfram, on the other hand, have demonstrated that this test cannot properly serve to answer this question, because the specificity of this procedure is so high that positive results can be achieved only with antigens that are chemically completely identical, and not with antigens that are biologically equivalent but chemically somewhat different. The immune-biologic relationship that exists between a protein and its derivatives—called "species specificity"—cannot, therefore, be shown by the Schultz-Dale method. But it can, on the other hand, be demonstrated by the following skeptophylactic animal experiments.

When a guinea pig allergized to egg-white, for example, is given a small amount of egg-white intravenously three weeks later, it promptly dies of anaphylactic shock. If, however, the shock dose is preceded by four intravenous injections of egg-white propeptan, in doses of 1 mg., 5 mg., 10 mg., and 20 mg., respectively, at intervals of five minues, the animal has only slight transitory symptoms.

Despite the chemical differences between proteins and propeptans, as well as the results of Schultz-Dale tests, the fact that skeptophylactic protection can be afforded only by biologically closely related agents proves that these derivatives have retained their species specificity. Nadel[19] undertook an exhaustive experimental investigation of this controversial question and came to the conclusion that the oral administration of partially digested protein for skeptophylactic purposes, as in propeptan therapy, has genuine theoretic and experimental foundation. Numerous authors (Bauer; Brandt; Chajes, von Eiselsberg; von Eiselsberg und Kauders; Freund; Hauramoto; Hecht; Hermann; von Hoesslin; Hopkins, Waters, and Kesten; Kaemmerer; Kauders; Kitamura; Markin; Rehfuss; Reiss; Rusten, Senn; Shay; Singer; Schreiber; Schreus; Ulrich; and others) report lasting results obtained with this method within two to three weeks of treatment. Others, however (including Bray, Rowe,

Vaughan, C. White), had no success with this method. This difference in results achieved may be explained by the fact that the first group of authors employed the original propeptans, while the latter employed their own preparations.

Propeptan therapy is our choice for the control of every type of hypersensitiveness to food proteins, irrespective of the clinical manifestation of the condition, such as asthma, rhinopathy, urticaria, or colitis.

The same principle of skeptophylaxis is the basis of the treatment of hay fever with grass pollen, provided the given allergen is administered three to four times daily. Many investigators, including Black, Thommen, Gatterdam, Stier and Hollister, Rockwell, Bohner, Alperstein, Schwartz, Iliff and Gay, and Thiberge have reported good or satisfactory results. On the other hand Bernstein and Feinberg, Forman, Zeller and a coöperative group under the direction of Feinberg hold the results of oral pollen therapy to be definitely inferior to those obtainable by parenteral administration of pollen extract.

Since whole pollen quite often causes distressing gastro-intestinal symptoms, Urbach treated pollen by digestion in order to free it of its native protein, while retaining its species specificity. It will be seen that the same reasoning was followed here as in the preparation of food propeptans. Hence, in 1931, Urbach introduced digests of pollens consisting largely of peptones, for the oral treatment of hay fever. If the pollen propeptans are individually compounded in accordance with the outcome of the tests on the patient, the results are very satisfactory.

SUMMARY

The most important anti-allergic methods are hyposensitization and de-allergization. The difference between these two approaches is a qualitative, not a quantitative, one.

In hyposensitization the antibodies circulating in the blood are markedly increased, thereby binding substantial quantities of antigen, thus preventing a cellular antigen-antibody reaction and therefore the occurrence of allergic manifestations. However, when the administration of antigen is stopped, the free circulating antibodies are gradually eliminated, but the tissue antibodies remain. Hence renewed contact with the antigen will again bring on an antigen-antibody reaction in the tissues, with its allergic consequences.

In de-allergization, the tissue-antibodies are neutralized or otherwise rendered incapable of reacting. This results first in the consumption of cellular antibodies and later in the arrest of the production of specific antibodies. In this manner, the entire organism (or the principal shock tissues) is rendered non-sensitive permanently or for a certain length of time. The object of de-allergization, therefore, is to convert the organism from the existing state of high antibody titer to one of normal antibody level. In other words, to change a hypersensitive individual into a normal one.

As to the practical application of de-allergization measures, the peroral and subcutaneous methods only are recommended.

There is some evidence that methods of hyposensitization under certain conditions, particularly if carried out for a number of years, may ultimately lead to de-allergization.

SUMARIO

Los más importantes métodos anti-alérgicos son los de hiposensitización y "de alergización." La diferencia entre estos dos ataques es cualitativa, y no cuantitativa. En hiposensitización, los anticuerpos que circulan en la sangre se aumentan con rapidez, con eso, se unen cantidades de substancias, de los antígenos así, impide una reacción antígena-anticuerpo celular y por lo tanto, ocurren las manifestaciones de alergia. No obstante, cuando la administración de antígenos impide a los anticuerpos libres que circulen, gradualmente, pero los anticuerpos del tejido permanecen. De aquí, el contacto renovante con el antígeno causando de nuevo una reacción antígena-anticuerpo en los tejidos, con sus consecuencias de alergia.

En la "de-alergización," los tejidos-anticuerpos se neutralizan o de otra manera la reacción es imposible. Esto resulta, primero, con el consumo de los anticuerpos celulares y, después en la cesación de la producción de los anticuerpos específicos. De esta manera, el organismo entero (o el "shock principal" de los tejidos) viene hacerse insensitivo permanentamente o por algún tiempo. El objeto de la "de-alergización," por lo tanto, es convertir el organismo del estado que existe en el "titre" anticuerpo alto al nivel del anticuerpo normal. En otras palabras, cambiar un individuo hipersensitivo a uno normal. En cuanto, a la aplicación práctica de las medidas "de-alergización," el peroral y el método subcutáneo son los únicos recomendados. Hay evidencia que los métodos de hiposensitización bajo ciertas condiciones, particularmente si se practican por algunos años, pueden finalmente conducir a la "de-alergización."

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THE CHEMISTRY OF RAGWEED POLLEN EXTRACT III

The Relationship of the Amount of Nitrogen Precipitated by Heat Coagulation, with Various Protein Precipitants, in Saline Ragweed Extract

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HEAT coagulation has been used as a method for separating protein from non-protein material.[1] It has also been used to separate various proteins from each other when the conditions for their coagulation are very different. In this paper we have attempted to establish a relationship between the amount of nitrogen precipitated by heating a saline ragweed extract to 100° C, with other common protein precipitating agents, when the same extract was used throughout. In this manner, any effective variable effecting heat coagulation would be the same. We have not tried to separate the various proteins by changing the pH, or ionic strength.

Since the active substance in ragweed pollen extract has not yet been isolated, we thought that subjecting the extract to boiling would help elicit two important groups of facts. First, if the material is albuminous in nature, we ought to be able to measure its concentration with qualitative accuracy. Second, if the active albuminous substance is said to be measured by any other method, our present studies could be used to corroborate the accuracy of these other methods of measurement. In order to measure the concentration of the albuminous fraction or fractions, the following experiments were performed.

A ragweed extract containing three grams of defatted pollen to 100 ml of 0.85 per cent saline was used throughout the studies. The extraction was done for twelve hours under toluene and at room temperature. The extract was centrifuged in order to remove all undissolved material. Of this extract, 50 ml. were heated to boiling. A definite flocculation was apparently complete at 100 C. The precipitated material was removed by centrifugation. Another 50 ml. of the extract was taken, unchanged, and both lots were Seitz filtered. This filtration was performed in order to keep the extracts sterile, and because it is a standard procedure when working with pollen extracts. Total nitrogen and protein-nitrogen determinations according to the method of Cooke and Stull[2] were done on both portions of the extract.

From Table I it can be seen that the values of the total nitrogen in the heated and unheated extracts were respectively 0.56 and 0.59 mg. per ml. The protein-nitrogen values were respectively 0.20 and 0.25 mg. per ml., the difference being 0.05 mg. per ml., the equivalent of 5,000 protein-nitrogen units. The difference between the total nitrogen in the heated and

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TABLE I. THE COMPARISON OF THE TOTAL NITROGEN IN HEATED (100 C) AND UNHEATED EXTRACT

Type of Extract	Total Nitrogen mg. ml.	Protein-Nitrogen mg. ml.
Heated	0.56	0.20
Unheated	0.59*	0.25

*Adsorption of nitrogen compounds by the Seitz filter pad accounts for the lower value of total nitrogen.

unheated was only .03 mg. per ml., but it must be remembered that albumin is adsorbed by the Seitz filter pad and that the values are comparable.

These results confirm those of Stull and others[8] who state that boiled extract loses the equivalent of 5,000 protein-nitrogen units.

Another extract made in the same manner and treated in the same way gave similar precipitate equivalent to 5,000 protein-nitrogen units. Other portions of this extract were treated with specific tests for albumin.[3] These results, shown in Table II, point to the fact that all the precipitating agents specific for albumin gave comparable values ranging from 4,000 to 6,000 protein-nitrogen units.

TABLE II. THE EFFECT OF VARIOUS PROTEIN PRECIPITATING REAGENTS ON THE AMOUNT OF NITROGEN PRECIPITATED

Reagent	Mg. Nitrogen ml.	Protein Nitrogen Units
1. 20% trichloroacetic acid	0.06	6,000
2. Sulfosalicylic acid	0.05	5,000
3. Tanret's reagent	0.06	6,000
4. Robert's reagent	0.04	4,000
5. Sodium chloride acetic acid	0.05	5,000
6. 66% ethyl alcohol	0.06	6,000
7 .66% acetone	0.06	6,000

The determinations listed in Table II were done in the following manner:

1. To 2 ml. of ragweed extract in a test tube was added 2 ml. of 20 per cent trichloroacetic acid, and the tube was immersed in boiling water until the precipitate had flocculated. The mixture was cooled and centrifuged, the clear supernatant fluid being carefully removed by means of a capillary and an aspirator pump. The precipitate was dissolved in 1 per

cent sodium hydroxide and transferred to a kjeldahl flash for a micro-nitrogen determination.[5]

2. To 2 ml. of ragweed extract was added 2 ml. of sulphosalicylic acid reagent. The mixture was immersed in boiling water until flocculation became visible, the remainder of the procedure being that for the determination given above.

3. To 2 ml. of ragweed extract was added drop by drop 1 ml. of Tanret's reagent. The precipitate was flocculated by heat, and the procedure given above, then followed.

4. To 2 ml. of ragweed extract 1 ml. of Robert's reagent was added drop by drop, the procedure given above then being followed.

5. To 2 ml. of ragweed extract 1 ml. of saturated solution of sodium chloride was added and one drop of acetic acid. This was placed in a boiling water bath, and after flocculation, the determinations given above were performed.

6. To 2 ml. of extract 4 ml. of absolute ethyl alcohol was added, and the mixture placed in a bath of boiling water. After flocculation, the usual procedure was followed.

7. To 2 ml. of extract 4 ml. of acetone was added, the mixture being heated in a water bath to cause flocculation, and the usual nitrogen analysis as outlined above was performed.

DISCUSSION

Hubbard and Osgood[6] used 20 per cent trichloroacetic acid to precipitate the active component of ragweed pollen extract. Seibert[7] clearly demonstrated that trichloroacetic acid was specific for albumin even in the presence of other fragments of protein molecules. The facts synopsized in Table II point to the belief that the amount of material precipitated by the different reagents specific for albumin is constant in amount. This constancy supports the hypothesis that the same material is being precipitated from each lot of extract. It is not great in amount, confirming the work of Heyl[4] who showed that the albumin content of ragweed was small.

If 0.00001 milligrams of this material is taken as a protein-nitrogen unit, the values for any extract should not range higher than 4,000-6,000 such units. Extracts standardized by the Cooke-Stull method[2] give higher readings because the phosphotungstic acid, as shown in other papers of this series, precipitates other substances, both protein and non-protein. It must be stressed at this point that the precipitated albuminous material is not the sole active substance in ragweed pollen extract, and that the foregoing experiments cannot, therefore, be used as the starting point for a method of standardizing pollen extracts.

CONCLUSIONS

1. The application of heat to a saline ragweed extract precipitates a constant amount of nitrogen.

2. Other precipitating agents specific for albumin all remove the same amount of nitrogen-containing substances from ragweed pollen extract.

3. The true albumin content of ragweed is small and under the conditions of this experiment is equivalent to about 5,000 protein-nitrogen units.

CONCLUSIONES

1. La aplicacion del calor a un extracto salino de ambrosia artemisifolio atrae una cantidad constante de nitrógeno.

2. Otros agentes específicos para el albúmen todos estos quitan la misma cantidad de nitrógeno de substancias contendidas del extracto pólen de la ambrosia.

3. El verdadero contenido de la ambrosía albúmen es menor y, bajo las condiciones de este experimento equivale a 5,000 unidades de proteína-nitrógeno.

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DERMATITIS VENENATA

(Continued from Page 138)

pleo. De los 2,544 pacientes, 1,748 éstos no faltaron ni un día a sus ocupaciones Por causa de la dermatitis venenata.

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THE EFFECT OF BETA-HYPOPHAMINE AND SUPRARENAL CORTEX EXTRACTS ON THE PREVENTION OF HISTAMINE SHOCK IN THE GUINEA PIG

A Preliminary Report

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THE possibility of an antagonistic effect of the hormones of the posterior pituitary pressor factor and suprarenal cortex is suggested when one compares their physiologic action with that of histamine.

As is well known, two active principles have been isolated from the posterior lobe of the pituitary gland: (1) Vasopressin, which acts on the circulation, producing arteriolar and capillary constriction (pressor action) and diminishes the urinary flow (antidiuretic action); (2) Oxytocin, exerting a stimulating action, principally on the uterus.

Extirpation of the adrenal cortex profoundly disturbs the mineral metabolism, the sodium level of the plasma is diminished, the potassium level is increased and the plasma volume is decreased, causing an increase in the concentration of the total solids, plasma proteins and hemoglobin, with increased tissue fluid. These changes can be prevented or corrected by the administration of cortical extract.

Histamine is a powerful capillary dilater and also dilates the arterioles. There is increased capillary permeability, with escape of plasma proteins into the extracellular fluid spaces, disturbance of mineral metabolism and hemoconcentration.

EXPERIMENTS*

Guinea pigs, selected from good stock and comparatively uniform in weight, on balanced rations, in an air-conditioned animal laboratory† were treated as follows: Twenty-one female guinea pigs, whose weights ranged from 320 to 375 grams (average 356 gms.), were used for determining the lethal dose of a solution of histamine dihydrochloride in normal saline. This was found to be fairly constant—0.1 c.c. of 1:100 dilution (0.66 mg. histamine base) when injected subcutaneously, symptoms of shock coming in four to seven minutes with death in four to twelve minutes.

From the same stock, seven pigs, overaging 360 grams each, received one dog unit of suprarenal cortex extract subcutaneously and 10 c.c. of physiologic normal saline intraperitoneally three hours preceding lethal doses of histamine dihydrochloride subcutaneously. Histamine shocks in these pigs were delayed to an average of one-half hour as compared with

*For these experiments, Pitressin (Beta-Hypophamine, each c.c. containing 10 pressor units) and Eschatin (suprarenal cortical extract, each c.c. containing 25 dog units), Parke, Davis and Company, were used.
†Pillsbury Flour Mills Research Laboratory.

those receiving lethal doses of histamine, but they all died in more violent shock than when treated with histamine alone; whereas, four out of seven pigs, whose average weight was the same and who received one unit of posterior pituitary pressor extract three hours before receiving a lethal dose of histamine, showed either no evidence of shock or very slight shock and apparently seemed to suffer no ill effects.

Autopsies of these pigs, dying in histamine shock, showed the characteristic changes of histamine poisoning, simulating anaphylactic shock —marked engorgement of the lungs with hemorrhages, increased mucous secretion, tissue edema, et cetera.

COMMENTS

Clinical observations, as well as these few preliminary animal experiments would indicate that there is no rational therapy for the use of suprarenal cortex hormone in allergic states.

The action of the posterior pituitary lobe extract, however, of constricting arterioles and capillaries and diminishing the loss of fluid by inhibiting the urinary flow with an accompanying slow rise in the blood pressure, would logically be expected to have an antagonistic action to a cholinergic drug such as histamine. This evidently occurred with the few animal experiments done. A combination of epinephrine with pituitrin is marketed as asthmolysin or epinephrine-pituitrin compound in the belief that pituitrin or posterior lobe extract prolongs or enhances the action of epinephrine; however, in those patients having acute asthma who do not respond to even large doses of epinephrine, the combination will sometimes be found to be somewhat more effective. This may be the result of an antagonistic action to histamine.

COMENTARIO

Las observaciones clínicas, tan bien como los primeros experimentos preliminares que se hicieron indicarían que no hay terapéutica racional en el uso del hormón suprarenal en condiciones alérgicas. La acción del extracto del pituitario posterior, sin embargo, las constricciones arteriolas y vasos capilares que desminuyen la cantidad de flúido, inhibiendo la orina y una elevación en la presión de la sangre, lo que naturalmente, supondría tener una acción antagonística a una droga colinérgica tal como "histamine." Esto con el tiempo ocurrió con algunos experimentos que se hicieron con animales. Una combinación de "epinephrine" con "pituitrin" que se conoce in el mercado como "Asthmolysin" o el compuesto de "epinephrine-pituitrin," con la creencia de que el extracto de "pituitrin" o lóbulo posterior prolonga la acción de "epinephrine." Sin embargo, en caso, de una asma aguda la cual no responde aun en dósis mayores de "epinephrine," la combinación se encontrará algunas veces siendo más efectiva. Esto puede ser el resultado de una acción antagonística de la "histamine."

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HISTAMINE BY MOUTH IN THE TREATMENT OF VASOMOTOR RHINITIS

By Julian C. Gant, Raymond J. Savignac and Adolph Hochwald

(Condensed from the New England Journal of Medicine by permission of the publishers)*

The authors at the Allergy Clinic of the Massachusetts General Hospital studied the effect of the oral administration of histamine on forty-six cases. Histamine is absorbed from the gastro-intestinal tract and produces the same physiologic reactions as does the parenteral injection. Therapeutic oral dosage varies with patients but remains quite constant over a long period of time. Their method is to start with one drop of a 1:1,000 dilution in a glass of water, on an empty stomach, and the reaction noted. (Too large a dose will aggravate the symptoms, too small a dose will cause no change and the correct dose relieves the patient within fifteen to twenty minutes.) If no bad effect, the patient is advised to increase the dosage one drop each day until toxic effects appear. Thereafter, he receives a maintenance dose, just below the toxic level, which is repeated as is necessary to control symptoms. Dosage may vary from one drop of 1:1,000 dilution to twenty-five drops of 1:100 dilution, the average being five to seven drops of the 1:1,000 dilution. Oral histamine therapy was given only when other methods of treatment were unsuccessful. The most striking beneficial effects were obtained by those with vasomotor rhinitis, symptomatic relief being obtained in ten to twenty minutes. With recurrence of symptoms, another dose is taken. Immediate symptomatic relief is the main objective and the histamine is needed less frequently as time goes on. Case reports and the occurrence of good results in all except two of thirty cases would indicate the results to be more than a coincidence. The dosage being delicate and the varieties in absorption great, it is necessary to observe rigidly basic conditions; menstruation may be affected by it. The method is not a panacea but brings results superior to other methods of symptomatic relief.

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Editorial

A la Profesión Médica de los Países Latino-Americanos*

DEDICAMOS ESTA SEGUNDA EDICIÓN de los "ANNALS OF ALLERGY" (Anales de Alergia), publicación oficial del Colegio Americano de Alergistas, a nuestros colegas latino-americanos a quienes saludamos muy cordialmente.

Admitiendo que dada la situación actual de las diversas agrupaciones médicas, éstas necesitan adoptar nuevos métodos de cooperación y mayor solidaridad, este Colegio propone atentamente a todos aquellos médicos que emplean la Alergia en su práctica professional, así como a cualquier científico que hubiese aportado su valiosa colaboración a nuestros conocimientos de Alergia, la organización de una alianza para defender nuestros intereses comunes. Al ofrecer esta idea, el Colegio plenamente reconoce y asímismo agradece a los eminentes científicos de esos países sus excelentes trabajos sobre Inmunología y Alergia.

Persiguiendo los afanes de otras especialidades en medicina, este Colegio está sumamente interesado en el intercambio de datos científicos pertinentes a una especialidad como la Alergia con médicos de otros países fuera de los Estados Unidos.

A este efecto, ya tenemos la buena fortuna de contar en esta asociación con celebrados Alergistas del Dominio del Canadá.

Para su más amplio conocimiento, le enviamos adjunto parte de los objetivos del Colegio, según se exponen en la primera edición de los "ANNALS." Este Colegio desea vivamente que se sirva honrarnos con su solicitud para hacerse bien socio activo, o Compañero Corresponsal, y de este modo contribuir a la futura expansión del Colegio.

F.W.W.

EL COLEGIO AMERICANO DE ALERGISTAS†

— Objetivos y Propósitos del Colegio —

El Colegio Americano de Alergistas fué incorporado en Noviember, de 1942, como una sociedad sin ninguna utilidad pecuniaria. Los objetivos y propósitos del Colegio son los siguientes:

(a) El establecimiento de una sociedad de médicos y científicos competenes se congregarán de vez en cuando para promover y avanzar el estudio, la investigación científica, y el conocimiento clínico de la alergia tocante a las varias especialidades en la medicina.

(b) Para mantener y adelantar las mejores normas posibles entre aquellos que ejercen la alergia.

(c) Para perpetuar las buenas tradiciones de la medicina y de su ética.

*An English translation of this editorial appears on page 170.

†The English version of this section of the above editorial appeared in the July-August issue, pages 63-65.

(d) Para establecer normas de calificación y procedimiento para la certificicación a los médicos dedicados a la especialidad de la alergia.

(e) Para mantener la dignidad y eficiencia de esta especialidad en su relación al bienester del pueblo.

(f) Para promover el trato amigable de áquellos dedicados a la práctica de la alergia.

Como primer objetivo del Colegio es beneficiar la alergia y los alergistas, para avanzar conocimientos e intereses de esta especialidad y representar la majoría de áquellos quienes se dedican seriamente en las soluciones de los problemas en este campo. Puesto que la alergia se hallará practicamente en toda especialidad en medicina y cirurgía, el propósito del Colegio es reconocer debidamente a los otolaringologistas y oftalomologistas, pediátricos, dermatólogos, gastro-enterologistas, también para los que ejercen la medicina interna aplicando la alergia en su prática. Ya que, muchos de los contribuidores prominentes que se hallan entre los inmunologistas, bacteriologistas, (micólogos), farmacólogos, bioquímicos, botanistas, patólogos (de botánica) etc., estos médicos deben recibir debido reconociminto siendo electos, como miembros de la confraternidad del Colegio. Todos los médicos en la sociedad serán médicos que ejercen alergia y los miembros se compondrán del otro grupo ya mencionado. La valioso consulta, servicios y consejos de aquellos (médicos) serán disponibles a todo tiempo mientras se cumplan las funciones y, compilando la publicación oficial del Colegio.

Hay más de dos mil médicos en los Estados Unidos, y sus posesiones, Canadá y la América-Latina quienes están aplicando y desarrollando los principios de la alergia a sus pacientes. Estos médicos representan las varias especialidades así como al práctico general quien realizará el mayor número de enfermidades de alergia.

El Colegio representa una cantidad de socios mayor que ninguna otra sociedad existente de alergia en los Estados Unidos, y los objetivos y propósitos desde el principio de su organización han progresado y ya han sido aceptados y relativamente en un tiempo corto a saber:

1. Considerar la alergia como una especialidad, entonces ha de ser análoga con cada otra especialidad de medicina.

2. Reconocer propiamente aquellos médicos serios y diligentes que ejercen la alergia como también a cualquier científico quien ha hecho valiosas contribuciones a nuestro conocimiento de alergia.

3. Unificar, harmonizar y centralizar, sin perder la identidad o el abuso de los derechos de las varias sociadades de alergia en los palses de Norte y Sur América de estos formando ya un solo Colegio con una perspectiva clara en la última definición como manifestada por los otros Colegios para el propósito de establecer normas específicas para la prática de alergia.

4. Rendir normas metódicas para el diagnóstico y tratamiento de las condiciones de alergia por medio de un laboratorio central para tales propósitos, como también, un departamento statístico de información para cualquier subjeto pertinente a la alergia.

5. Por medio de las facilidades de algunos de los socios y el laboratorio central se harán posible un curso para entrenar y reconocer a los técnicos de laboratorio en procedimientos en alergia, como también estudios postgraduados para todos sus miembros.

6. La diseminación de conocimientos que pertenecen a la alergia, por medio de una revista que tendrá departementos, representando todas las fases del sujeto.

7. El establecimiento de una Fundación por medio de donativos por personas ricas o victimas gratas de la enfermedad quienes desean promover nuestro conocimiento y alcance de la alergia.

8. Habrá una junta anual y si posible también asambleas locales, del Colegio. Entonces las varias sociedades de alergia participarían para el propósito de presentar artículos sobre la investigación científica y repasar cursos prácticos de alergia.

El Colegio ya ha establecido un laboratorio central que hace extractos "standardizados" diagnósticos, para el uso exclusivo de sus miembros, para que aquellos hagan uso de este servicio, usando extractos uniformes y así obtendrán resultados uniformes, comparables, a lo que antes jamás se había atentado. Este laboratorio central se mantiene sin utilidad monetaria, a base cooperativa y no compitirá con ninguna firma biológica. Tan pronto como las firmas biológicas reconozcan su importanica y manufacturen antígenos "standardizados" y, los caules serán aprobados por el Colegio Americano de Alergistas.

La publicación oficial del Colegio, "THE ANNALS OF ALLERGY" se publica bimensualmente, la primera edición fué la de Julio-Agosto de 1943. Esta es una revista de cien páginas dedicada a todos los sujetos tocante a la práctica de alergia. La "Junta de Directores" se compone de especialistas quienes han hecho contribuciones personales y dignas de mensionar, y sus ramos particulares: los practicantes de medicina interna, pediátricos, dermatólogos, otolaringologistas, gastroenterologistas, neurólogos, botánicos etc., El precio por subscripción de la revista "THE ANNALS" es $6.00 Dls. por año, en la cual se incluye los honorarios anuales.

Como habrá una bibliografía completa de las publicaciones de alergia y materia aliada, también habrá un índece publicado, el cual proporcionorá referencia permanente.

EXTRACTOS DE LOS ESTATUTOS DE LA SOCIEDAD

Clasificación de los Miembros

La Constitución provee Miembros de cuatro clases:
Artículo IV, sección 1.

(a) Miembros Honorarios;
(b) Miembros Activos;
(c) Miembros Asociados;
(d) Miembros Corresponsales.

Artículo IV, sección 2.

(a) Miembros Honorarios: Miembros en la organización serán los que, por razón de caracter personal, prominentes en su práctica, contribuciones meritórias a la investigación de alergia, Posiciones de influencia y honor, o éxito elevado en la ciencia de la alergia o en el arte de la medicina, han sido recomendados por el "comité de credenciales" a la "Junta de Directores" por su especial distinción.

(b) Miembros Activos: Serán miembros de la profesión médica dedicados como prácticos, profesores, o investigadores en el campo de la alergia, quienes habrán sido electos de acuerdo con estas constituciones y tales reglas adicionales como la "Junta de Directores" los acepte. Los primeros honorarios anuales del Colegio serán la suma de $50.00 Dls., $40.00 Dls. por adelantado al hacer la aplicación para hacerse miembro y la suma adicional de $10.00 Dls. pagable cuando el certificado de los miembros sea presentado. En caso de rechazamiento de un aplicante que falle inadmisión con los requisitos del Colegio $35.00 Dls. del depósito inicial se devolveran.

(c) Miembros Asociados: Cualquier científico que haya hecho contribusiones meritórias a la alergia es eligible para hacerse, miembro asociado en la Corporación. Honorarios anuales para los socios serán $10.00 Dls. por año pagados en adelantado.

(d) Miembros Corresponsales: Miembros corresponsales del Colegio serán electos por la "Junta de Directores" bajo la constitución. Y tales reglas como

las prescriba la directiva de entre el numero de contribuidores sobre alergia en otros países, esta selección puede hacerse por los residentes en los territorios y posesiones del Canadá y América-Latina.

Calificación de los Candidatos

Artículo IV, sección 4.

(b) El candidato debe ser a lo menos de 29 años de edad, debe ser graduado de un Colegio de medicina aprobado por el Concilio Educativo de Medicina y hospitales de las asociación médica de los Estados Unidos.

(c) El Candidato que ha practicado activamente la alergia por lo menos tres años antes de su nominación como miembro.

(d) El nombre de cada candidato será propuesto oficialmente.

(e) Credenciales adicionales se aplicarán a la eligibilidad del candidato para hacerse miembro así incluirán sus cualidades profesionales ya sean de hospital o académicas o acceptabilidad personal de miembros en su territorio, por lo cual han establecido su reputación, caracter y posición ética y actividades y, también atender a las juntas anuales del Colegio.

(f) Los Credenciales se aplicarán a la eligibilidad del candidato para hacerse miembros, pueden incluir publicaciones acceptables; una tésis sobre una investigación original; o un número razonable de papeles clínicos que serán requeridos por el "Comité de Credenciales." Estos papeles clínicos serán completos en toda forma por una referencia especial para el sumario diagnóstico y terapéutico.

(h) Para ser electo como Miembro se require primeramente dos tercios de votos del "Comité de Credenciales" y luego serán sometidos a la "Junta de Directores," y se require dos tercios de votos de los miembros de la "Junta de Directores."

(i) Los candidatos electos se las avisará inmediatamente de su elegibilidad.

Artículo VI, sección 9.

El "Comité de Registro" de Alergia. Este Comité determinará la naturaleza y caracter de la estatística de los socios en su funcionamiento de su práctica de alergia. Este Comité también está autorizado para establecer un departamento de información basada sobre la información adquirida por la estatística para la diseminación a los miembros del Colegio.

Artículo IX, sección 4.

El Colegio presentará un premio en efectivo, o material al socio que contribuya más y se distinga en la labor de la alergia dicho premio se dará el año anterior.

A Real Program

IT begins to seem that the initiative, courage, imagination and readiness to look ahead for the future of allergy by the American College of Allergists is being appreciated. The other two national allergy societies, The American Association for the Study of Allergy and The Society for the Study of Asthma and Allied Conditions are considering an amalgamation. The organization of other Allergy Forums is under consideration. These efforts are very encouraging for the future of allergy and allergists, and such coöperative methods are most commendable. It is earnestly hoped, since many of the members of the College belong to

these other groups, that the time will soon come when all can be united in one large national allergy society and their official publications become a single unit. It is only in this way that we can help each other to the greatest extent in furthering the specialty of allergy. Just recently, David Dietz, science editor of the Scripps-Howard newspapers, commented upon diminishing allergy research due to the fact that many allergists are in the service doing work in other fields. He states, "A great deal has, of course, been done in the last twenty years to understand and treat allergies, but we have learned during the present war how scientific progress can be speeded up when funds and trained men are made available for a piece of research. The number of men specializing entirely in allergies in peacetime did not exceed a few hundred. There is obviously room for much work in this field in the days after the war." One large national society composed of members who are making every effort to be honest and sincere with everyone when furthering the cause of allergy can make unbelievable strides in investigative and clinical allergy, once these younger scientists can again direct their efforts along these lines. We need a firm research foundation, centralization of efforts, and organized unity before allergy will attain its proper position in medicine.

F.W.W.

SIXTH ANNUAL FORUM ON ALLERGY

An international postgraduate society organized in response to an apparent demand, the American Forum on Allergy was founded in 1938 at Cincinnati, Ohio, as a midwest organization of allergists, to provide a place in which to review the progress of clinical allergy, provide in the present time a forum for the younger men, and offer intensive postgraduate instruction to physicians working in allied fields.

Annual meetings have been held each year since in the following cities: Toledo, Ohio (1939); Chicago, Illinois (1940); Indianapolis, Indiana (1941); Detroit, Michigan (1942); Cleveland, Ohio (1943).

In 1940 the name was changed to the Annual Forum on Allergy to correspond with the international character of its attendance, and the Forum Gold Medal was established for outstanding contributions to clinical allergy. The first recipient was Béla Schick, the second, W. W. Duke, and the third, Arthur F. Coca.

The sixth Annual Forum will be held in the Statler Hotel in St. Louis on Saturday and Sunday, January 22 and 23, 1944. This is a meeting in which all reputable physicians, who are interested in the subject, are offered the opportunity of bringing themselves up to date in this rapidly advancing branch of medicine. The two days are devoted to intensive postgraduate instruction.

Attention is called to the fact that during these two days almost every type of instructional method is employed. Special lectures are presented by outstanding authorities, and group studies, exhibits and pictures complete the program.

Although the program is most intense, informality and an emphasis on the practical mark the conduct of the whole meeting. Good fellowship reigns during the dinners, luncheons and smokers throughout the two days. For a copy of the program write to: Jonathan Forman, M.D., 956 Bryden Road, Columbus, 5, Ohio.

Correspondence Items

Hair Lacquer Dermatitis

In a personal communication recently, Dr. J. Bedford Shelmire of Dallas, Texas, reported that he has had no less than ten cases of dermatitis caused by hair lacquer. Also, Dr. William Clark, a dermatologist of this city has had six such cases; Dr. C. M. Griswold one, and I one of a similar nature. Dr. Michael Zeller of Chicago has had three cases and Dr. F. W. Wittich of Minneapolis, one. In each instance, it was caused by the application of Hubere Lacquer Pads, produced by the Hubere Cosmetic Company of Chicago. All these patients presented severe cases of contact dermatitis. The ears looked like those of a pugilist; the eyes were swollen shut and a violent erythema was present about the neck. It has also been observed that one may get a negative patch test on the arm but when placed on or near the neck, the reaction is not only positive but may be severe.

Dr. Louis Schwartz, Medical Director Chief, Dermatitis Investigation Section, U. S. Public Health Service, informs me as follows: "Upon investigation, we found that three concerns in Chicago were selling these lacquer pads—Hubere Cosmetics, Parfait Powder Puff Company, and Trylon Products. The irritant agent was a synthetic resin made from a combination of rosin and fumeric acid, in one instance, and maleic anhydride, rosin, and ethylene glycol, in the other. The resulting compounds were used as a substitute for shellac, which is no longer obtainable."

RALPH BOWEN, M.D., Houston, Texas.

Contact Dermatitis of Legs from Street Car Seats or So-called Street Car Rash

During the summer months of 1943 in Cleveland, several patients have complained of a "street car rash." They describe symptoms of intense itching in the posterior proximal portion of both thighs where the skin comes in contact with the street car seat. Some of these seats are wooden and others are of leather composition or straw. It is a certain type of straw seat these patients have been in contact with, and to date we have been unable to get patch testing material for making further investigation. The lesions were urticarial in type and would last for a period of a few minutes to several hours, depending upon the length of time that the patient was on the street car or the amount of exposure. It seems to be common knowledge that many young women riding in the street car in the Summer without stockings and coming in contact with these seats describe the dermatitis as "street car rash"; this is their terminology which is rather descriptive. The patients question a cleaning solution used on these seats.

I wonder if other men have made similar observations or have had comparable histories?

J. WARRICK THOMAS, M.D., Cleveland, Ohio.

Control of Weed Growth Now Possible

Any procedure which aims at the control of weed growth is of practical interest to allergists. "Sinox" is the trade name of the sodium salt of dinitrol cresol. This product was originally developed in France and was used primarily as a medical agent for reducing weight. After injurious effects and even deaths were noted from its use, it was discarded for this purpose. It was accidentally discovered

very effective in controlling the growth of weeds. It has a selective action in that it rolls off the grass leaves but adheres to the rougher surface of the weed leaves. It is particularly effective when used as a spray upon the smaller weeds early in their growth. It kills ragweed and similar weeds but not the grass of the small grains. The Department of Agronomy, Department of Agriculture, University of Minnesota, finds that it is very effective in spraying the flax fields in controlling wild mustard. It is claimed by the manufacturer to be a fungicide and is recommended for controlling "athletes foot." It would seem, however, that the usual precautions should be taken by the user in preventing inhalation of the spray. It is a very intense yellow dye and will permanently stain woolen clothing but will readily wash out of cotton goods so that cotton clothing should be worn when spraying with the solution. One gallon of the original solution is mixed with 100 parts of water and is used as a spray. This amount will cover one acre and sells for about $2.25 per gallon.

F. W. WITTICH, M.D., Minneapolis, Minnesota.

Seasonal Bronchial Asthma in a Dog

It is well known that allergy may manifest itself in lower animals. Wittich reported a case of a dog having seasonal hay fever during the ragweed season (J. Allergy **12**:247, 1941). This animal had certain intracutaneous tests made, and a colored movie was made of the reactions as well as the symptoms experienced by the dog.

Recently, I had a patient who had seasonal bronchial asthma during the hay fever season. During the consultation, she gave me a detailed history of the experience that she had had with her dog. The dog suffered repeated asthmatic attacks limited to the ragweed season for 3 years. The onset of symptoms would occur between August 14 and 17 and continue throughout the hay fever season. This animal was a shorthaired Scotch terrier crossed with a Spitz.

The patient reported that a patent medicine, "Dr. Tucker's Asthma Inhaler," had relieved seasonal episodes of asthma. On occasions when the dog had had severe seasonal asthmatic attacks he was also given inhalations of Dr. Tucker's asthma medicine. The patient had taken ephedrine pills with some symptomatic relief of her symptoms, and the dog had experienced similar relief of his symptoms on the same medication. The animal also had hay fever with considerable itching and watery rhinorrhea, and it was necessary for the patient to use Kleenex frequently for the dog. She also used Vick's nose drops, with some slight symptomatic relief. She felt that the use of Vick's salve applied to the dog's throat or chest made him more comfortable and that the hay fever and asthma were less annoying.

As far as could be determined, the animal had no evidence of cardiac involvement or edema, and the symptoms were entirely limited to the ragweed season, except that during the winter months if he contracted an acute respiratory infection he developed asthmatic bronchitis.

Each time the dog would lie down under ragweed plants in the patient's yard, he would have a definite exacerbation of his trouble. This animal had x-rays and an examination by the local veterinarian, including complete x-rays of the teeth. He lived to be 14 years of age. The cause of death was thought to be old age and not in any way related to his allergy, as his death occurred out of pollen season.

As this animal was not seen by an allergist, there was no opportunity for an investigation of his sensitivity to the pollens, but it was an interesting observation made by this patient who had a comparable seasonal bronchial asthma.

J. WARRICK THOMAS, M.D., Cleveland, Ohio.

Abstracts

PROGRESS IN ALLERGY

The Sulfonamides and Allergy

ETHAN ALLEN BROWN, M.R.C.S. (London), L.R.C.P. (England), F.A.C.A.

The manifestations of sulfonamide sensitivity are so protean, and the literature so voluminous that it is impossible to review all of it in any one paper. There have, however, been a number of papers in the last four years which seem to give a complete picture, and they have, however, been chosen for the following review.

In 1938, Tedder[28] described three types of dermatoses resulting from the use of sulfanilamide therapy. Among others are listed: (1) A skin manifestation precipitated by exposure to ultraviolet light; (2) a sensitivity to the drug associated with intolerance to further dosage; (3) a toxic dermatosis resulting from cumulative effect or diminished excretion. The skin reactions may take maculopapular, urticarial, scarlatiniform, and purpuric forms.

Haviland and Long[19] studied seventy-eight patients, of whom ten developed skin eruptions and six showed reactions of the conjunctivæ. Schnee[25] described a patient, an officer in the U. S. Army Tank Corps, who was given sulfathiazole orally for five days in the treatment of an upper respiratory infection. The patient, on the sixth day, presented a sore mouth and cracked lips. On the seventh day, there was inflammation of the nasal mucosa and a recurrence of temperature. The treatment with sulfathiazole was then resumed, but the inflammation of the eyes, nose, and mouth grew worse. When the sulfathiazole was discontinued, all the mucosal lesions disappeared.

To the various types of skin manifestations previously described, Applebaum and Bachrach[1] added two cases in which there was a fine vesicular eruption with discrete lesions of minute, elevated, white vesicles, each of which was surrounded by a red areola, the vesicles being found chiefly on the torso, but also on other parts of the body. The same patient showed an injection of the conjunctivæ and a nodular eruption as well.

This nodular type of eruption has been studied by Loveman and Simon.[27] Their patient had been given sulfanilamide for gonorrhea and responded with a typical erythema nodosum as confirmed by microscopic examination. This patient was tested intracutaneously upon both normal and previously diseased areas with a saturated solution of sulfanilamide, with a tissue extract of an active nodule, and with blood serum containing a high concentration of the sulfonamide drugs. The tests and patch tests were all negative. The lesions, however, could be elicited at will by the administration of sulfanilamide.

Another type of rash was added to the list of skin manifestations by Raffelto and Nichols.[23] Their patient, a ten-year-old girl, was given sulfadiazine and responded with pyrexia, toxemia, and a dermatological lesion resembling pemphigus. The medication had been administered for eight days. No sulfadiazine was given for four days, but two days after the beginning of its second administration, the patient had the reaction described. There was a concomitant eosinophilia of 23 per cent.

Other organs besides the skin were soon found to respond abnormally to sulfonamide ingestion. Whitehouse and Bargen,[31] in the Proceedings of the Staff Meetings of the Mayo Clinic, reported upon a forty-two-year-old patient who, on four separate occasions following the administration of sulfathiazole, responded with fever, and a typical athralgia. It is interesting to note that in these four successive courses of treatment, the drug was administered for fourteen days during the first period, ten days for the second, five days for the third, and one day for the fourth.

Discontinuation of the sulfathiazole therapy caused immediate remission of the symptoms. There were no skin lesions of any type with sulfathiazole, and at a later date when the patient was given sulfaguanidine and also saccinyl sulfathiazole, there were no abnormal reactions.

Sensitivity to only one of the sulfonamide drugs with tolerance to another had previously been noted by Goodman and Arthur.[10] Their patient, a negro, could take sulfapyridine with impunity, but following the administration of sulfanilamide, he showed a fixed-drug eruption, described as a macular patch surrounded by concentric rings of vesicles, undoubtedly deep in the skin. This patient was negative to patch, scratch, intracutaneous, and passive transfer tests with sulfanilamide.

Another negro patient, reported upon by Davidson and Bullowa,[5] became sensitive to sulfapyridine and also to sulfamethylthiazole. In this case, the patient who had lobar pneumonia was given 12 grams of sulfapyridine. Two days later he was able to take sulfapyridine again for four days, following which there was an unexplained rise in temperature. The drug was discontinued, but eleven days later, following the ingestion of 5 grams of sulfamethylthiazole, the patient manifested, within three hours, a severe reaction, associated with chills, fever, a generalized pruritus, conjunctival injection, and a scarlatiniform eruption. One week later, a similar reaction was elicited with only one-tenth the previous dose of sulfamethylthiazole as well as by a small dose of sulfapyridine. This same patient evinced no reaction whatsoever to sulfanilamide.

A similar type of reaction was described by Nelson.[20] His patient took sulfathiazole with no ill effects, but seven months later, following a second ingestion, had a typical reaction with malaise, headache, nausea, and pyrexia. This same patient responded in the same way to sulfadiazine and to sulfanilamide.

Along these lines it is interesting to note that in 1940 Wedum[29] prepared sulfonamide and sulfapyride azoproteins according to Landsteiner's method, coupling both substances to beef serum. The azoproteins were used to produce anaphylactic and cutaneous sensitivity to guinea pigs and also precipitin in rabbits. The results showed that sulfanilamide and sulfapyridine azoproteins can produce heterologous antibodies for each other, although the homologous are always stronger than the heterologous reactions. The animal sensitized with the sulfapyridine azoprotein reacted more to the sulfanilamide azoprotein than the animal sensitized to sulfanilamide reacted to sulfapyridine. The sulfathiazole azoproteins did not form precipitates with sulfanilamide or with sulfapyridine azoprotein anti-serums. Sulfanilamide azoprotein anti-serum gave the highest precipitin titres. The uncombined sulfanilamide compounds could not be used as immunizing or testing antigens, but sodium sulfapyridine inhibited the sulfapyridine and sulfanilamide azoprotein precipitins without affecting the precipitins for the beef sera.

Drugs so far emphasized in this paper have been the sulfonamides in usual practice, especially sulfanilamide and sulfathiazole. The newer sulfonamide derivatives are, however, not free from side-effects. Hall and Spink[12] reported recently upon the toxic manifestations of sulfamerazine which they used in one hundred and sixteen patients. In three of these there was a secondary fever, undoubtedly due to the drug, and in two of the fever patients, there occurred a maculo-papular rash scattered over the entire trunk and the extremities. The fever and the rash both subsided when the drug was discontinued. In one patient, a child, there was a transient leukopenia and a granulocytopenia.

The literature describing these unusual responses gives us no clear-cut method for testing for sensitivity. A patient described by Loveman and Simon[17] presented cutaneous lesions of the palms and the back of the neck two weeks after he had taken 10 grains of sulfanilamide for ten days. A second course of treatment caused stomatitis, new cutaneous lesions and also a lighting up of the cutaneous sites previously affected. Patch tests with a solution of the sulfanilamide were positive on

those areas of the skin which had been previously involved, but negative on normal skin sites. Passive transfer could not be demonstrated. The patient evidently had his skin lesions following all administrations, and gave local patch tests but only on the affected areas of the skin.

On the other hand Kalz and Steeves[15] reported two cases in which 30 per cent sulfathiazole in a glycerin base had been applied for sycosis barbæ. Each application of the drug caused a local edema and an oozing dermatitis. One of the patients, following oral administration, developed edema of the face and a generalized pruritis. The other developed an edema of the face and hands. In these patients, patch tests with sulfanilamide, sulfathiazole, sulfapyridine, and sulfadiazine powders were all positive, but again only on the diseased areas. These patients had evidently been sensitized by cutaneous application.

Four cases of cutaneous hypersensitivity to topical applications of sulfonamides were reported by Weiner.[20] The patients responded to topical applications of sulfathiazole and sodium sulfathiazole ointments with a skin condition, described as resembling contact dermatitis, the initial lesions being a papule or a vesicle which passed through the stage of eczematous oozing, erythema, crust formation, desquamation, and final restitution without scars. Patch tests established the diagnosis. Two of the patients were not sensitive to other sulfonamide drugs. No note is made whether or not the patch tests were on diseased or normal skin. There are many other reports of hypersensitivity produced by topical applications. Among these must be mentioned the paper by Sams and Copland.[24] Their case was one of a recurrent contact dermatitis following surface application of sulfathiazole powder. Sulfathiazole given orally precipitated a severe reaction in the areas previously treated topically, as well as a general eruption. Patch tests were negative. Five patients treated by Miller[19] responded to sulfathiazole ointment with typical contact dermatitis. One responded in the same way to ingestion which caused a generalized eruption, most severe at the site of the original surface application. Shaffer[26] described four more cases of contact dermatitis following topical application of sulfathiazole with exacerbations on ingestion. In his patients, tests by the Praustnitz-Kustner technique gave both immediate and delayed reactions. A staphylococcal infection may have been a predisposing cause.

To extend the list, Cohen, Tomas, and Kalisch[4] reported on two cases in which 5 per cent sulfathiazole ointment applied for varicose ulcers of the legs resulted in fever and a generalized rash. In both cases, the patients were sensitized so that oral administrations of one eighth of a grain of sulfathiazole caused the rash to reappear six hours after ingestion.

Statistical studies by Livingood and Pillsbury,[16] reporting on more than a thousand patients treated locally with sulfonamides, show twelve cases presenting characteristic systemic and dermatologic sulfathiazole reactions following local applications of a 5 per cent ointment for more than five days and becoming evident after oral administration.

The obverse picture, however, has also been seen. Patients seem to be able to stand topical applications when they are sensitive to oral administration. Green and Steckle[11] used sulfathiazole in a 5 per cent ointment locally, and gave the same patient the same drug orally for the treatment of a staphylococcus leg lesion. After 7 grams of the drug had been taken, the patient responded with a fever and a generalized morbilliform rash. The oral administration was, therefore, discontinued, but the local applications were used for thirty-two more days with no reaction, although blood studies showed that the absorption of the drug reached almost 1 mg./100 cu. mm. of blood. This patient had oral reactions following sulfapyridine but was definitely not sensitive to sulfanilamide or sulfadiazine.

The sensitivity acquired by local treatment of sulfonamides may evidently last for some time. MacGregor[18] reports that such sensitivity may last at least fifteen

months, the area affected reacting to topical application and ingestion. The patient, twelve months previous to the report, had grazed his left knee which was treated with 5 grams of sulfanilamide daily for two and a half months. Three months later an attack of acute follicular tonsillitis was treated with sulfanilamide. Fifty-six hours later, the area on the left knee, previously affected, responded with a dermatitis. At the time the patient was seen, a deeply grazed buttock wound was treated with local applications of sulfanilamide powder. Twenty-four hours later, the same area of the knee was red, and twelve hours later, discharging.

The blood manifestations of sulfonamide sensitivity should not be lost sight of. As early as 1939, Dolgopol and Hobart[6] described three cases of severe granulocytopenia following sulfapyridine, and in 1941, Goldman, Applebaum, and Antropol[9] described two cases of fatal agranulocytosis following sulfapyridine, adding these to the twenty-eight cases of malignant neutropenia following the use of the same drug previously listed in the literature. Recently Hurd and Jacox[14] described two cases of thrombopenic purpura, the first sensitive to sulfathiazole, and the second, to sulfadiazine.

A case report from the Charlotte Memorial Hospital[3] of a death apparently due to sulfathiazole, reporting that the patient died after the administration of 18 grams of sulfathiazole, mentioned that the patient had probably had sulfonamide therapy for gonorrhea the previous year. It is urged that patients who have had sulfonamide therapy be told exactly what drug they were given and how much, so that on future occasions the information would be available to physicians who wished to use the same type of treatment for a second time.

The photosensitization of patients taking sulfonamides has been studied by Epstein.[7] He was able to perform twenty-two experiments on six subjects, eliciting two different types of skin reactions following the intradermal injection of 0.1 c.c. of a 1 per cent solution of sulfanilamide, followed in twenty-four hours by irradiation by ultraviolet light. The first reaction following exposure was a typical ultraviolet erythema. The second type of reaction, however, appeared spontaneously on the tenth day in two of the subjects, and showed itself as an inflammatory urticarial lesion associated with intense pruritus, appearing at the site of the original reaction and persisting for two weeks. Subsequent tests on the same two subjects produced a similar lesion, appearing in ten to twenty-four hours.

Epstein's work was confirmed by Blum[2] who took the investigation one step further, showing that the active wave-length was shorter than 3200A. The response was not concerned with porphyrins. Clinical confirmation was on a somewhat statistical basis as published by Park and Platts.[22] Their report concerned itself with 486 soldiers in the Middle East who received sulfanilamide and 309 who were given sulfapyridine. Of the first group, twenty-one (4.3 per cent) and of the second group, six (1.9 per cent) developed a light dermatitis eight to ten days after the drug was first administered, the parts of the body being most affected being those which were exposed to the light. In many cases, the dermatitis subsided in two to four days, and treatment could be resumed if the patients were not exposed to sunshine. One hundred Moaris, treated with sulfa drugs, presented no photosensitivity. Among the white patients, those who had areas of the skin which were sun-tanned showed these areas to be the least affected. One-third of those patients who developed the dermatitis were found to be highly susceptible to ultraviolet radiation.

Erskine[8] suggests that the rash due to sensitization may be distinguished from that due to drug retention and describe the test by which such differentiation may be made. He feels that occurrence of sensitization may be minimized by therapeutic restriction to seven days or less. Photosensitization may be prevented by avoiding exposure to light during the course of therapy. He feels, with Park and Platts, that further medication may be continued safely in patients who can be shielded from ultraviolet radiation.

ABSTRACTS

As the sulfonamides become more and more widely used for the prophylaxis of upper respiratory infections and for minor skin conditions, greater numbers of the population will undoubtedly become sensitized, and such sensitivity, in the future, will undoubtedly bring to our attention not only more cases of sensitivity but other types of sensitivity which may be so rare that they have not yet been recognized or described. Although the common types of sensitivity are now easily recognizable, it is not common knowledge that there are at present available more than 2,500 derivatives of sulfanilamide. These have been reviewed by Northey[21] who classifies them by name, giving for each its theoretical action and probable future developments. Time will undoubtedly see the list of sulfonamide drugs in actual use indefinitely extended, each bringing with itself its own problems of possible sensitization.

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Questions and Answers

Letters of inquiry should contain the writer's name and address; however, these will be omitted when requested. Competent allergists, when answering these questions, wish it to be understood that it does not represent the opinions of any official group.

Has the inhalation of sulfonamides been used in the treatment of respiratory allergy?

M. D., Wisconsin

Biancani (1940) demonstrated experimentally that inhalation of nebulized solutions of the drug resulted in its deposit through the tracheobronchial tree and within the alveoli. Castex et al. (1941) confirmed these experiments and reported favorable results with nebulized solutions of sulfonamides in the treatment of broncho-respiratory disorders. In this country, with the exception of the use of nebulized solutions of bronchodilating drugs in the treatment of bronchial asthma or where the systemic effects of epinephrine are desired in the treatment of other allergic states, little use has been made of this mode of introduction of drugs. Barach et al. experimentally used the method for the introduction of promin in the treatment of tuberculosis. Stacey (Diseases of the Chest, **9**:302, 1943) reports the use of the inhalation of nebulized solutions of sulfonamide in the treatment of bronchiectasis.

Osgood (1942) reported that of the sulfonamides, sulfathiazole had the most marked bacteriostatic effect. The experiments of Stacey and his coworkers of a similar nature indicated that sulfathiazole was the drug preferred for local use in the lungs. The method of administration is similar to the one used when treating asthmatics with bronchodilator solutions (Richards, Barach, et al.). One cubic centimeter of a 5 per cent solution of sodium sulfathiazole is used in a nebulizer connected by a rubber tube to an oxygen tank equipped with a flow meter. Five or six liters of oxygen per minute will nebulize 1 c.c. of this strength solution in twenty minutes to one-half hour. The nostrils are not plugged, and the patient holds the nebulizer between the teeth and breaths with the mouth open. Stacey advises the initial treatments to be administered slowly and cautiously. In his experience, however, he did not observe the patient to show any signs of irritation to the membranes, such as coughing, et cetera. The sodium sulfathiazole precipitates out as sulfathiazole when in contact with body fluids. One to three treatments a day are given over a period of many weeks; no evidence of local irritation or systemic effects from the use of the drug have been reported. Measurable amounts of the drug do not appear in the blood. According to Stacey treating bronchiectasis with sodium sulfathiazole by means of inhalation of nebulized solutions is an easy and effective treatment for the disease.

Five cases of bronchiectasis complicating pulmonary tuberculosis were reported where toxic symptoms subsided, cough and expectoration were greatly lessened or disappeared, as well as the dyspnea. Sputums which were frankly purulent would become definitely diminished in amount and thin and mucoid in character.

Since there have been beneficial results reported from systemic use of the sulfonamides in the treatment of bronchial asthma complicated by infection, the local use of sodium sulfathiazole would appear to be rational therapy in certain cases. Watson and Kibler (Journal of Allergy, **10**:364, 1939) noted the high percentage of allergy in a relatively large group of bronchiectatic patients. They reported beneficial results when recognizing these food sensitivities and placing these patients under allergic management. In the so-called intrinsic asthmas

where infection plays a role, especially of the respiratory tract, and there is an associated chronic bronchitis or bronchiectasis, the use of nebulized solutions of sodium sulfathiazole may be of use. On the supposition that local bacterial antigens are destroyed by the drug, it would appear that there is an indication for the trial of such therapy in certain selected cases.

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What is the proper hypodermic dose of adrenaline (epinephrine hydrochloride 1/1000) for an infant under one year of age who has attacks of bronchial asthma unrelieved by other medication?

Unfortunately, there is no practical weight-dose formula for adrenaline at this or at any other age, since the individual response is so variable. The proper dose at any age is that which gives the maximum therapeutic response with a minimum of disagreeable side reactions. It must be remembered that infants are more readily shocked by adrenaline than older individuals, and extreme care must be employed in the use of adrenaline in infancy.

At this age one should start with 0.10 c.c.; if no relief, 0.15 c.c. may be given in fifteen or twenty minutes; if no relief then, the dosage may be increased by increments of 0.05 c.c. every fifteen or twenty minutes until relief or until it is evident by the usual symptoms of adrenaline fastness that the infant will not respond. At this age the amount is usually not over 0.20 to 0.30 c.c. though rarely a higher dose is necessary and is well tolerated. Should the infant respond favorably to a given dose, a note should be made as to the amount so that it may be used as a starting dose in case of subsequent attacks.

To the Medical Profession of the Latin-American Countries

(Translation of Spanish Editorial appearing on page 157.)

THIS, THE SECOND ISSUE of the ANNALS OF ALLERGY, the official publication of The American College of Allergists, is dedicated to our Latin-American Colleagues to whom we extend most cordial greetings.

Recognizing that new conditions in the various medical groups require new cooperative methods, and a closer unity, the College extends a sincere invitation to those applying Allergy to their medical practice as well as any scientist who has made valuable contributions to our knowledge of Allergy, in an alliance of our common interests. When extending this solicitation the College fully recognizes and is grateful for the outstanding contributions made to Immunology and Allergy by brilliant scientists of your countries.

In accordance with the efforts of the other specialties in medicine, the College is very desirous for an interchange of scientific information concerning the specialty of Allergy with physicians in countries other than the United States of America.

We are fortunate in having excellent Allergists from the Dominion of Canada in the organization.

For your further information, herewith is included in part the objectives of the College as set forth in the first issue of the ANNALS. It is earnestly hoped that the College may be honored with your application for active, associate, or corresponding Fellowship, so that we may share in the further development of the College.

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College News

(Items of interest about Fellows of the College will be appreciated)

First Lt. Philip M. Gottlieb, M.C., has been assigned to organize, operate and service the Allergy Clinic at the Northington General Hospital, Tuscaloosa, Alabama, under the Fourth Service Command.

Lt. Comdr. Edward L. Alexander, M.C., U.S.N.R. was a recent visitor in the central office. He is now on assignment in physical medicine for the United States Navy at the Mayo Foundation.

It is hoped that the many members of the College in the service will write in from time to time some of their experiences for the informal correspondence column.

Owing to unavoidable circumstances as the result of difficulty in obtaining supplies, the framed membership certificates for the members of the College will be delayed for a very short period. We hope to have them reach all of the members, except those who are overseas, before the next issue of the ANNALS.

Major Alex. A. Friedlaender, M.C., A.U.S. (Retired) announces his association with Dr. Meryl M. Fenton, 1212 Eaton Tower, with practice limited to Allergy.

Coöperation of the College with the military authorities and assisting in the supplying of physicians with special training in Allergy for our war needs, has been greatly encouraged by Col. S. W. French of the Fourth Service Command, who is in charge of the seventy-seven Allergy Stations in the Fourth Service Command of the United States Army.

It has been made possible recently to send to men in the service medical books or medical journals overseas by a recent Regulation (Order 1967 Supplementary Note) under the date of March 12, 1943, supplementing a previous Postal Regulation to this effect. Therefore, those of you who have medical friends overseas can send them books of current interest on the subject of allergy, as well as otherwise. If you should have difficulty in getting the postmaster to accept such a parcel, it is because he is not acquainted with the recent regulation, and you can adjust the difficulty by consulting the superintendent of mails. These packages can be sent regardless of the weight if they are medical books.

Baylor University College of Medicine moved to Houston, Texas, from Dallas, and classes began in the temporary quarters on July 12, 1943. The college received a grant of one million dollars from the M. D. Anderson Foundation for the erection of the Medical College building. The building will be erected as soon as possible upon a twenty-acre campus site, which is a part of a plot of land set aside for the Texas Medical Center. A grant of another million dollars was received from the M. D. Anderson Foundation for research. One-third of the income from a two and a quarter million dollar trust donated to Baylor University by Mr. and Mrs. H. L. Kokernot has been assigned to the Medical College. The

Houston Chamber of Commerce has pledged fifty thousand dollars yearly for ten years.

The medical profession and the people of Houston have extended a warm welcome and the fullest coöperation to the College.

Drs. Ralph Bowen and Homer E. Prince are among the new members of the Clinical staff. They accepted the positions of Associate Professor of Clinical Medicine (Allergy).

There will be a meeting of the Board of Regents of the College at the Hotel Gibson in Cincinnati on the morning of November 16. The Southern Medical Association, with general headquarters at the Hotel Netherland-Plaza, is meeting November 16, 17, and 18. There will also be a meeting of the Editorial Board of the ANNALS OF ALLERGY on the morning of Wednesday, November 17, as well as an informal meeting of all of the Fellows at the Hotel Gibson on the evening of November 17. Further details will be posted at the meeting.

It is unlikely that there will be a national convention of the College until after the duration. The functions of the organization will be carried on by committee meetings, when central and convenient, as is the Southern Medical Association meeting. Conventions at the present time are difficult to organize and attend (crowded hotels, difficult transportation, etc.). Also, most of the men in the service, which includes about one-third of the membership, will not be able to be present. It is very important that at this first meeting there should be a representative vote since nine members of the Board of Regents shall be elected from and by the Fellows of the College (Article V, Section 1) and "all officers shall be elected by the Fellows of the College at their annual meetings" (Article V, Section 7 of the By-Laws). It is also desirable, as soon as practical, to have the applicants for membership selected by a majority vote of the College at large, based upon the findings as to the qualification of candidates by the Credentials Committee to the Board of Regents. It is obvious that during the period of organization many functions otherwise must be assumed by the organizers until that time when additional By-Laws can provide for a more proper representation of the College as a whole. The increasing applications for membership by some of the most outstanding personalities in allergy since the appearance of the first issue of the ANNALS, would indicate confidence in its officers to carry on for the duration.

Since the first issue of THE ANNALS contained special announcements necessary in initiating such a journal, some of the features proposed by the editorial board were omitted for lack of space. It is intended that a couple of pages in the ANNALS OF ALLERGY be devoted to sectional problems in allergy. In other words, the United States and Canada, the South American states, will be divided into about ten zones, with some one as correspondent requesting interesting occurrences at particular seasons in their respective areas which may have a bearing upon the local problems of allergy. For example, many of the southern states have had hay fever appearing three or four weeks earlier than usual, and many patients were miserable sufferers this spring. This season does not correspond with a clean cut, tree or grass pollinating season when the pollens of both plants would be expected in the air in abundance. A Committee for the Study of the Unknown Causes of Hay Fever and Asthma in the South, as well as the formation of the Southwest Allergy Conference, is now actively engaged in investigating this problem.

Derbes has also recently shown that the pollen of the linden or basswood, an insect borne pollen, appears in certain localities in large numbers. It is a buoyant

pollen and is partly air borne. Derbes has shown that linden pollen can produce hay fever. It occurs in the northern states, including Canada, and may be a factor from Maine to the Dakotas and southward nearly to the Gulf, and extending eastward to Delaware including the western portion of the southern states except Florida. Again, soil erosion experts of the United States Department of Agriculture have caused the farmers of the Dakotas and other sections of the middle northwest to plant brome grass in large amounts, not only to prevent soil erosion but because it is an excellent cattle grass. This is now becoming a factor in the grain belt of the Northwest, which has its local problems of grain mill dust, grain molds and grain insects as shown by others.

Durham has shown that Kochia pollen is becoming more widespread and of increasing clinical significance in areas where the pollen was heretofore unimportant.

Since most of the problems of allergy are local problems, it would be proper that there should be a geographical zoning so that there may be a more systematic survey of those local factors which may be important allergens.

The journal also proposes starting a series of articles biographical in character, brief and of a personality sketch type, accompanied by a photograph of the outstanding pioneers of allergy in this country.

The finances of the College are becoming well established. The funds are deposited in one of the oldest established banks in the Northwest, a certified public accountant is in charge of all bookkeeping, and those responsible are bonded.

As many Fellows of the College as possible are urged to attend the Sixth Forum on Allergy at St. Louis, January the twenty-third and twenty-fourth. The Midwestern Forum is one of the original sponsors of clinical allergy in this country and has a very definite function in continuing to arouse, encourage and instruct the young allergist of the future. It has become international in scope and fills an urgent need. Likewise, all local and sectional groups such as the Southwest Allergy Forum should receive our coöperative support. It is hoped that in the not too distant future the annual meetings of the College will have sectional representation from these various groups, at the same time having them maintain their original, complete and valuable identity.

A RAPID METHOD FOR THE PREPARATION OF ALCOHOL SPONGES

Among the various supplies employed in the practice of allergy the cotton alcohol sponge is one of the most commonly used. The preparation of the small round sponges requires time and labor. The following rapid method of preparation of sponges is suggested with the idea of saving time, labor and material.

The apparatus employed consists of a trimmer board such as that used in trimming photographic prints. The board is about 112 inches square and has a cutting knife on one side. These boards are manufactured by Burke and James, Inc., of Chicago, Illinois. The 12-inch size is designated as Rexo No. 3.

The sponges may be cut into one-inch square flat biscuits. In the process of cutting the edges are crimped. A second grade of cotton must be used. It may be obtained in one pound rolls, the strips being about 12 inches wide. Within a few minutes a 12 by 12 inch strip of cotton can be made into 144 sponges, using 24 strokes with the knife.

FRENCH K. HANSEL, M.D.

BOOK REVIEWS

Books listed here become the property of the College library when reviewed. A microfilm or miniature photostat service will be available to the members at cost. Members, however, are requested to write reviews on any book which may be of interest to allergists.

AN INTRODUCTION TO MEDICAL MYCOLOGY. Second Edition. By Geo. M. Lewis, M.D., and Mary E. Hopper, M.S. 342 pages. 79 illus. including 2 color plates. Price, $6.50. Chicago: The Year Book Publishers, Inc., 1943.

The second edition of this widely accepted, practical monograph on cutaneous mycology is just off the press. Additional plates and sufficient new data as the result of wide-spread fungus disease in the armed forces makes this edition welcome. Both the clinical and laboratory phases are presented concisely and in a clear readable style. The book is finished, accurate and practical, and should be useful not only to the specialist but to the profession at large. It is well bound, and the format all that could be expected by the severest critic. The photographs and photomicrographs, as well as the two full-page plates in accurate natural colors, represent the last word in published photography. Many new and additional subchapters are contained in this edition, and some of the chapters rewritten to bring our knowledge of fungus diseases to date. The chapter on the technique and interpretation of the passive transfer test has been completely revised, as well as the later data on the trichophytin, oidiomycin, coccidioidin, blastomycin and sporotrichin tests. Not only are the secondary allergic manifestations due to fungus infections of the skin (dermatophytids and moniliids) fully discussed, but the relation of asthma and hay fever to air-borne molds brings this phase of fungus sensitization to date. All physicians applying allergy to their practice will find the book a valuable aid. The diagnosis and treatment of the superficial mycoses and the deep mycoses (essentially systemic) are clear and specific. The most effective medications are presented by simple but detailed directions. The characteristics of pathogenic fungi and the practical points in laboratory technique make it comparatively easy for any physician with a bacteriological laboratory available to identify and treat any of the diseases caused by fungi. The book is an excellent example of what can be accomplished by completeness, accuracy and artistry. Both the authors and the publishers are to be congratulated.

F. W. W.

NERVOUSNESS, INDIGESTION AND PAIN. By Walter C. Alvarez, M.D., 488 pages. Price, $5.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers. 1943.

This book is by the same author as "An Introduction to Gastroenterology" by the same publishers. This is an unusual treatise written in a conversational, informal style for the most part narrating the author's experiences with that large group of patients manifesting nervous symptoms associated with their diseases, whether functional or organic. It is an excellent presentation of the method of handling that large group of patients complaining of "nervous indigestion." The gastroenterologists managing such cases must necessarily understand the fundamentals of psychiatry. The author, therefore, stresses the importance of taking an adequate history, and discusses at considerable length the proper management

of the common neuroses, functional digestive disorders, organic diseases sometimes manifesting the puzzling syndrome, the rare and poorly understood symptom-complexes, constitutional inadequacy and puzzling types of pain. Food sensitiveness or allergy is presented in a practical, succinct manner, annd should be read by every physician applying allergy to his practice. The author lays due stress upon the importance of allergy when discussing headaches, migraine, the irritable bowel syndrome, pseudo-ulcer, diarrhea, etc. The differential diagnosis and treatment of the various states are adequate. It is a book which should be read by the general practitioner as well as the specialist as it is a product of personal and independent thinking which fills an actual need.

F. W. W.

COMPENDIO DE ALERGIA CLINICA. Por el Doctor Enrique I. Shahon, F.A.C.A., médico oficial de la administración de Veteranos, Boston, Massachusetts; miembro honorario, de la sociedad Argentina de Alergia. Ex médico de la administración de Veteranos de los Estados Unidos, Aspinwall (Pittsburgh), Pennsylvania; asistente, del servicio oto-rino-laringologico del "Lincoln Hospital," N. Y.; instructor, del New York Post-Graduate Medical School and Hospital de la Universidad de Columbia. Versión única en español del original en inglés, inédito, traducida y adaptada por el eminente médico, el Doctor Guido Ruiz Moreno, jefe de la sección alergia, del Instituto de Investigaciones Fisicas Aplicadas a la Patología Humana, de la Academia Nacional de Medicina jefe del servicio de alergia del hospital Británico de Buenos Aires; miembro titular de la sociedad Argentina de Alergia; miembro correspondiente de la "American Association for the Study of Allergy"; miembro de "The International Correspondence Club of Allergy"; aspirante a profesor de Higiene y Medicina Social de la Facultad de Ciencias Médicas de Buenos Aires. Hay 335 páginas y 37 ilustraciones. Buenos Aires: Librería Hachette S.A., 1943.

Este libro está encuadernado en una forma útil y práctica de tipo compendio que fué introducido por el Doctor Arturo F. Coca, quien lo ha compilado de la literature que existe sobre el importantísimo problema de la medicina, con el aporte de sus vivos conocimientos y su experiencia prática. El autor ha logrado excepcionalmente bien, en seleccionar el establecído conocimiento fundamental de alergia, de la literatura original en inglés y arreglándola en un manual práctico. Este es un texto excelente para todos aquellos médicos quienes desean aplicar la alergia a su prática o especialidad. La etiología, patología, diagnóstico y terapéutica de todas las enfermedades alérgicas, basadas sobre nuestros conocimiemtos presentes, estos has sido presentadas claramente. Hay también capítulos sobre flora alergógena de Argentina por los Doctors Jose F. Molfino y Guido Ruiz Moreno, de Uruguay por el Doctor Guido Ruiz Moreno, y del Brasil por el autor basados sobre las observaciones de los Doctors A. Oliveira Lima y J. B. Greco. Esperamos que los impresores en corto tiempo tengan disponible una edición en inglés para que muchísimos más de la profesión médica puedan obtener suma ventaja de su uso.

F.W.W.

The English translation of the above review of "Compendio de Alergia Clinica" appears on page x of the Advertising section.